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Intermittent preventive treatment for malaria in children living in areas with seasonal transmission (Review)

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[Intervention Review]

Intermittent preventive treatment for malaria in children living in areas with seasonal transmission

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ABSTRACT

Background

In malaria endemic areas, pre-school children are at high risk of severe and repeated malaria illness. One possible public health strategy, known as Intermittent Preventive Treatment in children (IPTc), is to treat all children for malaria at regular intervals during the transmission season, regardless of whether they are infected or not.

Objectives

To evaluate the effects of IPTc to prevent malaria in preschool children living in endemic areas with seasonal malaria transmission.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register (July 2011), CENTRAL (*The Cochrane Library* 2011, Issue 6), MEDLINE (1966 to July 2011), EMBASE (1974 to July 2011), LILACS (1982 to July 2011), *m*RCT (July 2011), and reference lists of identified trials. We also contacted researchers working in the field for unpublished and ongoing trials.

Selection criteria

Individually randomized and cluster-randomized controlled trials of full therapeutic dose of antimalarial or antimalarial drug combinations given at regular intervals compared with placebo or no preventive treatment in children aged six years or less living in an area with seasonal malaria transmission.

Data collection and analysis

Two authors independently assessed eligibility, extracted data and assessed the risk of bias in the trials. Data were meta-analysed and measures of effects (ie rate ratio, risk ratio and mean difference) are presented with 95% confidence intervals (CIs). The quality of evidence was assessed using the GRADE methods.

Main results

Seven trials (12,589 participants), including one cluster-randomized trial, met the inclusion criteria. All were conducted in West Africa, and six of seven trials were restricted to children aged less than 5 years.

IPTc prevents approximately three quarters of all clinical malaria episodes (rate ratio 0.26; 95% CI 0.17 to 0.38; 9321 participants, six trials, *high quality evidence*), and a similar proportion of severe malaria episodes (rate ratio 0.27, 95% CI 0.10 to 0.76; 5964 participants, two trials, *high quality evidence*). These effects remain present even where insecticide treated net (ITN) usage is high (two trials, 5964 participants, *high quality evidence*).

IPTc probably produces a small reduction in all-cause mortality consistent with the effect on severe malaria, but the trials were underpowered to reach statistical significance (risk ratio 0.66, 95% CI 0.31 to 1.39, *moderate quality* evidence).

The effect on anaemia varied between studies, but the risk of moderately severe anaemia is probably lower with IPTc (risk ratio 0.71, 95% CI 0.52 to 0.98; 8805 participants, five trials, *moderate quality evidence*).

Serious drug-related adverse events, if they occur, are probably rare, with none reported in the six trials (9533 participants, six trials, *moderate quality* evidence). Amodiaquine plus sulphadoxine-pyrimethamine is the most studied drug combination for seasonal chemoprevention. Although effective, it causes increased vomiting in this age-group (risk ratio 2.78, 95% CI 2.31 to 3.35; two trials, 3544 participants, *high quality evidence*).

When antimalarial IPTc was stopped, no rebound increase in malaria was observed in the three trials which continued follow-up for one season after IPTc.

Authors' conclusions

In areas with seasonal malaria transmission, giving antimalarial drugs to preschool children (age < 6 years) as IPTc during the malaria transmission season markedly reduces episodes of clinical malaria, including severe malaria. This benefit occurs even in areas where insecticide treated net usage is high.

16 April 2019

Update pending

Studies awaiting assessment

The CIDG is currently examining a new search conducted up to 17 Jul, 2018 for potentially relevant studies. These studies have not yet been incorporated into this Cochrane Review.

PLAIN LANGUAGE SUMMARY

Administering antimalarial drugs to prevent malaria in children during the malaria transmission season

In areas where malaria is common, younger children have repeated episodes of malarial illness, which can sometimes be severe and life-threatening. In areas where malaria is seasonal, a practical policy option is to give drugs to prevent malaria at regular intervals during the transmission season, regardless of wether the child has malaria symptoms or not. This is known as Intermittent Preventive Treatment (IPTc).

The authors identified seven trials (12,589 participants); all were conducted in West Africa, and six of seven trials were restricted to children aged less than 5 years. The results show IPTc prevents three quarters of all malaria episodes, including severe episodes, and probably prevents some deaths.

Several antimalarial drugs or combinations have been tried, and shown to be effective. The most studied is amodiaquine plus sulphadoxine-pyrimethamine (AQ+SP). This combination probably doesn't have serious side effects but does cause vomiting in some children.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

IPTc compared with placebo for reducing malaria morbidity and all cause mortality

Patient or population: Children aged less than 5 years

Settings: Areas with seasonal transmission

Intervention: Intermittent Preventive Treatment of malaria

Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	IPTc				
Clinical malaria	**2.5 episodes per child per year** [3]	**0.7 episodes per child per year** (0.4 to 1.0)	**Rate Ratio 0.26** (0.17 to 0.38)	9321 (6 studies)	⊕⊕⊕⊕ **high** [1,2]	
Severe malaria	**35 episodes per 1000 children per year** [4]	**9 episodes per 1000 children per year** (4 to 27)	**Rate Ratio 0.27** (0.1 to 0.76)	5964 (2 studies)	⊕⊕⊕⊕ **high** [2]	
Death from any cause	**3 per 1000 per year**	**2 per 1,000 per year** (1 to 5)	**Risk Ratio 0.66** (0.31 to 1.39)	9533 (6 studies)	⊕⊕⊕⊖ **moderate** [5]	
Moderately severe anaemia	**67 per 1000 per year**	**47 per 1000 per year** (35 to 65)	**Risk Ratio 0.71** (0.52 to 0.98)	8805 (5 studies)	⊕⊕⊕⊖ **moderate** [6]	
Serious drug related adverse events	-	-	-	9533 (6 studies)	⊕⊕⊕⊖ **moderate** [7]	
Non-serious adverse events	-	-	-	9533 (6 studies)	⊕⊕⊕⊖ **moderate** [8]	

*The **assumed risk** is taken from the sum of events and participants in the control groups in the trials unless stated otherwise in the footnotes.

The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The included trials were conducted in children aged < 5 years in Ghana, Mali (2), The Gambia, Senegal and Burkina Faso. Three studies administered monthly AQ+SP, two studies used SP every two months, and one study used monthly SP + AS. Two studies which also distributed ITNs showed that these benefits remain even where usage of bednets is over 90%.

[2] There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.

[3] The incidence of malaria in the control groups was 2.25 episodes per child per year in Senegal, 2.4 in Mali, and 2.88 in Burkina Faso.

[4] The incidence of severe malaria in the control groups was 37 per 1,000 children per year in Mali, and 32 per 1,000 children per year in Burkina Faso

[5] Downgraded by one for imprecision: There were very few deaths in these trials, and none of the trials were adequately powered to detect an effect on mortality. Larger trials are necessary to have full confidence in this effect. However, a reduction in death would be consistent with the high quality evidence of a reduction in severe malaria.

[6] There was substantial heterogeneity between these five trials and the trials from Ghana and the Gambia did not show an effect. Downgraded by one for inconsistency. There was no reason to downgrade for study limitations, directness or precision.

[7] No drug-related serious adverse events are reported. Downgraded by one under precision as trials of this size are underpowered to fully detect or exclude rare serious adverse events.

[8] Downgraded by one under study limitations. All seven trials commented on observed adverse events. However, the thoroughness of the methods used to collect these data are incomplete in some of these trials. The only adverse event found to be statistically more common with IPTc was vomiting after AQ+SP

BACKGROUND

Malaria

Malaria, a disease common in both the tropics and subtropics, is caused by *Plasmodium* parasites transmitted to humans through the bite of infected female anopheline mosquitoes. People who live in or visit areas where malaria commonly occurs (endemic areas) are at risk of malaria infection. Infected people may show no sign of illness (asymptomatic malaria) or may develop fever, chills, malaise, and headache (symptomatic malaria). The severity of malaria infection varies from mild (uncomplicated) to life-threatening (severe). Among the five species of malaria parasites that infect humans, *Plasmodium falciparum* is the main parasite species responsible for causing severe malaria and is most frequently encountered in sub-Saharan Africa. People with severe malaria become very ill, may develop severe anaemia, convulsions, or become unconscious, and, in some cases, die.

Severe malaria is more likely to occur in people who possess low or no immunity to malaria (Gilles 2000). Children living in malaria endemic areas acquire natural immunity to malaria by the age of seven to 10 years old (Branch 1998; Warrell 2001). However, preschool children living in malaria endemic areas have inadequate immunity to malaria. This explains why the majority of the one million malaria deaths that occur each year in endemic areas of sub-Saharan Africa occur in this age group (WHO 2009).

Malaria control strategy

Malaria control aims to reduce illness and death from malaria infection. The World Health Organization's (WHO's) global malaria control strategy recommends a multi-pronged control approach that combines multiple preventive interventions with prompt diagnosis and treatment of symptomatic persons with efficacious antimalarial drugs (WHO 2000; WHO 2005). Artemisinin-based combination therapy (ACT) regimens have replaced chloroquine in most malaria-endemic countries as the first-line treatment for uncomplicated *P. falciparum* malaria, due to the widespread development of parasite resistance to chloroquine. The effectiveness of ACTs has been proven by several randomized controlled trials, but access to prompt ACT treatment has remained low in most parts of sub-Saharan Africa due to limited resources for health care (WHO 2005). Recent reports indicate that less than one-third of African children aged under five years who are sick with malaria receive prompt treatment with ACTs (UNICEF 2007).

Vector control is also another important part of the global malaria control strategy. The effectiveness of insecticide treated nets (ITNs) in reducing malaria morbidity and mortality in preschool children (Lengeler 2004) and pregnant women (Gamble 2006) has been confirmed, but coverage of this intervention in most sub-Saharan African countries lags far behind global targets. By 2009, less than one-third of the endemic countries in this region had attained 30% coverage for children under five years, far below the Roll Back Malaria (RBM) targets of 60% and 80% for 2005 and 2010 respectively (WHO 2009). Indoor residual spraying (IRS) is another vector control measure recommended by the WHO for community protection. However, it is expensive and requires high coverage to be effective (WHO 2006). Such high levels of coverage would be difficult to attain in many endemic areas, especially those with high perennial transmission.

Malaria prevention using drugs

Prophylaxis and IPT are two drug-based methods for preventing malaria. Prophylaxis refers to "the administration of a drug in such a way that its blood concentration is maintained above the level that inhibits parasite growth, at the pre-erythrocytic or erythrocytic stage of the parasite's life-cycle, for the duration of the period at risk" (Greenwood 2006). Drugs used for malaria prophylaxis are usually given in daily or weekly doses.

Intermittent treatment, also known as 'intermittent preventive treatment' or 'intermittent presumptive treatment' (IPT), is an alternative strategy and is defined as "the administration of a full therapeutic course of an antimalarial or antimalarial combination to a selected, target population at specified times without determining whether or not the subject is infected."(Greenwood 2010). While some experts believe that IPT is of benefit through some mechanism that is qualitatively different to prophylaxis, others suggest it is basically the same mechanism (White 2005).

Some scientists are concerned that prophylaxis in children may impair the acquisition of natural immunity to malaria and therefore make them more vulnerable to severe malaria when they grow older (WHO 1993). Previous research has shown that young African children who received malaria prophylaxis over an extended period of time had lower levels of malaria antibodies than their counterparts, although there is less robust evidence that this increased the risk of death from malaria later in life (Otoo 1988b; Greenwood 2004). Also, there are concerns that the widespread use of antimalarial drugs for prophylaxis in young children could increase the resistance of the malaria parasites to these drugs (WHO 1990; WHO 1993; Alexander 2007). However, the design of a randomized controlled trial will not detect this.

One of the assumed advantages of IPTc over prophylaxis, especially when used during a defined malaria transmission season, is the belief that short and intermittent use of antimalarial drugs for preventive purposes are unlikely to result in as much compromise of natural immunity as continuous prophylaxis (Greenwood 2010). Researchers have defined an area as having marked seasonality in malaria transmission if 75% or more of all malaria episodes occur within six months or less of the year (Roca-Feltrer 2009). IPTc is also likely to have fewer adverse events than prophylaxis because it is taken less often, and be easier to deliver through clinics (Aponte 2009).

IPT is now a recommended strategy for preventing the complications of malaria in pregnant women and infants living in endemic settings (WHO 2005; WHO 2010). IPT in these population groups is not included in this review but has been evaluated elsewhere (Garner 2006; Aponte 2009).

An earlier version of this systematic review addressed the broader question of the effectiveness of chemoprevention (including prophylaxis and IPT) against malaria in preschool children resident in endemic communities. Continuous prophylaxis is no longer included in this review, as attention has turned towards intermittent treatment strategies, but the details of prophylaxis trials are well documented in the previous versions of this review available from the archives of The Cochrane Collaboration (Meremikwu 2002, Meremikwu 2005, Meremikwu 2008).

Why it is important to do this review

IPTc has the potential to provide significant health benefits for pre-school age children, especially in areas of seasonal transmission. In order to provide reliable evidence to inform public health guidance and policy on this issue the need for a systematic review on this subject has become pertinent.

A further change in terminology has occurred recently, and the WHO now refer to IPTc targeted at areas of seasonal transmission as 'Seasonal Malaria Chemoprevention'.

OBJECTIVES

To evaluate the effects of Intermittent Preventive Treatment (IPTc) to prevent malaria in preschool children living in endemic areas with seasonal transmission.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials. The randomization unit may be the individual participant or a cluster, such as a household.

Types of participants

Children aged below six years living in an area where malaria is endemic with seasonal transmission. Children with unknown infection status (ie unknown whether each child was infected or uninfected) or known infection status, were eligible.

Trials that included only infants (age < 12 months) and trials that included only anaemic participants were excluded from this review.

Types of interventions

Intervention

- IPTc, defined as a full curative dose of an antimalarial alone or in combination given to children monthly or every two months during the malaria transmission season.

Control

- Placebo or no treatment.

Trials that allocated an additional intervention to both the intervention and control group were also included providing the additional intervention was the same for each group.

Types of outcome measures

Primary

- Clinical malaria (clinical feature of malaria with asexual peripheral parasitaemia of any density).

Secondary

- Severe malaria (as defined by WHO, (WHO 2000)).
- Parasitaemia.
- Death from any cause.
- Hospital admission for any reason.
- Severe anaemia (ie haemoglobin < 5 g/dL).
- Moderately severe anaemia (ie haemoglobin < 8 g/dL or haematocrit < 25%).
- Any anaemia (ie haemoglobin < 11 g/dL).
- Haemoglobin (or haematocrit).

Adverse events

- Serious adverse events (ie any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage).
- Non-serious adverse events (ie any adverse change in health or side effect that occurs in a person within the follow-up time of the trial, but is not a serious adverse event).

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Databases

We searched the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register (July 2011); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2011, Issue 6); MEDLINE (1966 to July 2011); EMBASE (1974 to July 2011); and LILACS (1982 to July 2011). We also searched the *meta*Register of Controlled Trials (*m*RCT) using 'malaria', 'child*', 'intermittent', 'prevent*' and 'IPT' as search terms (July 2011).

Researchers

We contacted researchers working in the field for unpublished and ongoing trials.

Reference lists

We also checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

Two authors (EE, CO) independently screened the results of the literature search for potentially relevant trials and obtained the full reports of the potentially relevant trials. Two authors (EE, CO) independently assessed their eligibility using a form based on the inclusion criteria. Each trial report was scrutinized to ensure that multiple publications from the same trial were included only once. The trial's investigators were contacted for clarification if eligibility was unclear. We resolved disagreements through discussion, and when necessary, by consulting a member of The Cochrane Infectious Diseases Group editorial team. We listed the excluded studies and the reasons for their exclusion.

Data extraction and management

Two authors (MM, EE) independently extracted data from the included trials using a data extraction form. We resolved disagreements through discussion by all four reviewers and, when necessary, by consulting a member of the Cochrane Infectious

Diseases Group editorial team. We contacted the corresponding publication author in the case of unclear information or missing data.

For each outcome, we extracted the number of patients randomized and the number analysed in each treatment group for each trial.

For dichotomous outcomes from trials that randomized individual patients, we recorded the number of participants experiencing the event and the number analysed in each treatment group. For continuous outcomes, we extracted arithmetic means and standard deviations, along with the number of patients analysed, for each treatment group. For each count outcome, we extracted a rate ratio with its standard error, however, when this information was not given we extracted the number of episodes and the number of person-years for each treatment group.

For trials that randomized clusters, we recorded the number of clusters in the trial, the average size of clusters, and the randomization unit (eg household or institution). The statistical methods used to analyse the trial were documented along with details describing whether these methods adjusted for clustering or other covariates. When reported, estimates of the intra-cluster correlation (ICC) coefficient for each outcome were recorded. When the trials' analyses had adjusted for clustering, we extracted the treatment effect and a corresponding measure of variability. Where the analyses were not adjusted for clustering, we extracted the same data as for the trials that randomized individual patients.

Assessment of risk of bias in included studies

Two authors (MM, CO) independently assessed the risk of bias of each trial using a risk of bias form. We attempted to contact the authors if this information was not specified or if it was unclear. We resolved any disagreements by discussion between review authors.

For trials that randomized individuals, six components were assessed: generation of the randomization sequence, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other biases (such as the trial stopped early). For trials that randomized clusters, additional components were assessed, that is, recruitment bias, baseline imbalances, loss of clusters, incorrect analysis and comparability with trials that randomized individuals.

Judgements of 'yes', 'no' and 'unclear' were made to indicate a low, high or unclear risk of bias. We presented the results of the assessment in a risk of bias graph, risk of bias tables and a risk of bias summary.

Measures of treatment effect

The risk ratio was used to summarise dichotomous outcomes, the mean difference was reported for continuous outcomes, and the rate ratio was used for count outcomes. All measures of effect were presented with 95% CI.

Unit of analysis issues

If the original trial analyses had not adjusted for clustering, we planned to adjust the results for clustering, by multiplying the standard errors of the treatment effect by the square root of the design effect. The design effect is calculated as 1+(m-1)*ICC where m is the average cluster size and ICC is the intra-cluster correlation coefficient. We planned to estimate the ICC from other trials included in the review or by contacting trial investigators.

Dealing with missing data

We aimed to carry out the analysis according to the intention-to-treat principle. However, when there was loss to follow up, a complete-case analysis was employed, such that, patients for whom no outcome was reported were excluded from the analysis. This analysis assumes that the patients for whom an outcome is available are representative of the original randomized patients.

Assessment of heterogeneity

We inspected the forest plots to detect overlapping CIs, applied the Chi^2 test and a P value of 0.10 was used as the cut-off value to determine statistical significance. We also estimated the I^2 statistic with values of 30 to 59%, 60 to 89% , and 90 to 100% used to denote moderate, substantial and considerable levels of heterogeneity respectively.

Assessment of reporting biases

We planned to explore publication biases by constructing a funnel plot providing sufficient studies contributed to the treatment comparison.

Data synthesis

We used Review Manager (RevMan) 5 for data analysis.

We stratified the analyses by whether the outcome was measured during intervention or postintervention.

We combined cluster randomized trials that adjusted for clustering with trials that randomized individual patients using generic inverse variance meta-analysis. We tabulated the results from cluster randomized trials that did not adjusted for clustering.

In the first instance, we applied a fixed-effect meta-analysis. However, if we detected a degree of heterogeneity but still considered it appropriate to combine the trials, we used a random-effects approach.

Subgroup analysis and investigation of heterogeneity

If heterogeneity was detected, we explored possible causes using subgroup analyses. Subgroups used were: type of antimalarial drug and additional interventions (no additional intervention versus ITN versus other).

Sensitivity analysis

We conducted a sensitivity analysis to investigate the robustness of the results to the risk of bias components by including only trials that concealed the allocation and had low incomplete outcome data (i.e. <10%).

RESULTS

Description of studies

Results of the search

We assessed the search results and included seven trials (see 'Characteristics of included studies'), and excluded 95 studies (see 'Characteristics of excluded studies').

Included studies

Location

All seven trials (12,589 participants) were conducted in West Africa: one in each of Burkina Faso, Gambia and Senegal; two in Ghana and Mali respectively.

Malaria endemicity

The pattern of malaria transmission was seasonal in all trial sites. Five trials reported entomological inoculation rates (infective bites per person per year): 173 bites (Konate 2011); from 1 to 177 bites (Sesay 2011), 65 bites (Kweku 2008), from 6 to 37 bites (Dicko 2011) and 10 bites (Cissé 2006). Two trials did not report entomological inoculation rates but described malaria endemicity as hyperendemic in the study areas (Dicko 2008, Tagbor 2011).

Trial design

Six of the trials randomized individuals, while one randomized clusters (communities) (Tagbor 2011). This trial adjusted for clustering in its analysis by analysing the data at the community level. The length of follow-up for the included trials varied from six months to two years; with one year being most common.

Interventions

All seven trials comprehensively used IPTc for the primary prevention of anaemia and malaria in healthy preschool children during malaria transmission seasons from three to six months.

The trial regimens consisted of:

- Standard treatment doses of sulfadoxine-pyrimethamine given monthly or every two months during the malaria transmission season (Dicko 2008; Kweku 2008),
- A combination of standard treatment doses of sulphadoxine-pyrimethamine and amodiaquine monthly for three consecutive courses during the peak malaria transmission season (Dicko 2011; Konate 2011;Sesay 2011),
- A combination of artesunate (4 mg/kg) plus amodiaquine (10 mg/kg) monthly or every two months (Kweku 2008; Tagbor 2011),
- A combination of the standard dose of sulfadoxine-pyrimethamine plus one dose of artesunate (4 mg/kg body weight) once monthly for three consecutive months (Cissé 2006).

Co-interventions

Two trials (Sesay 2011, Tagbor 2011) studied the effect of IPTc in areas where access to antimalarials was also being improved through home-based management of malaria (HMM).

Two trials (Dicko 2011, Konate 2011) administered IPTc alongside ITN distribution and promotion.

Outcomes

Clinical malaria: Six trials reported on incidence of clinical malaria, while one reported incidence of fever episodes without parasitological confirmation (Tagbor 2011). Trialists reported clinical malaria defined by different parasite density cut-off points and defined by any parasitaemia but we extracted data on clinical malaria with any parasitaemia. Two trials provided adequate information on severe malaria for meta-analysis. Clinical malaria and severe malaria were reported as incidence rates.

Anaemia: All included trials provided some data on anaemia but only five provided adequate information for inclusion in meta-analysis. (Cissé 2006; Dicko 2008; Dicko 2011; Konate 2011; Kweku 2008). All five trials reported data on moderately severe anaemia (haemoglobin < 8 g/dL or packed cell volume < 25%) but only two (Dicko 2011, Konate 2011) provided information on severe anaemia (haemoglobin < 5 g/dL). Three trials (Dicko 2011; Konate 2011; Tagbor 2011) provided data on mild anaemia (haemoglobin < 11 g/dL). Tagbor 2011 was a cluster-randomized trial and provided adequate information for calculation of design effect; anaemia data from this trial was therefore included in meta-analysis following adjustment for cluster design effect.

Other outcomes: Other relevant outcomes reported were death (six trials included in meta-analysis), hospital admission (three trials) and parasitaemia (six trials).

Adverse events: All trials reported on adverse events; information on adverse events are summarized in a table. Data on reported adverse events were included in meta-analysis if they helped to provide additional information to explain any remarkable differences observed between treatment and control groups.

Post-intervention (rebound) events: Data on post-intervention assessment of trial outcomes were included in meta-analysis if they were adequate; only a few trials provided adequate post-intervention data for meta-analysis. Three trials provided adequate information on incidence of clinical malaria post-intervention (Cissé 2006; Dicko 2008; Kweku 2008).

Excluded studies

The excluded studies and the reason for their exclusion are shown in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

See Figure 1 and Figure 2 for a summary of the risk of bias assessments.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

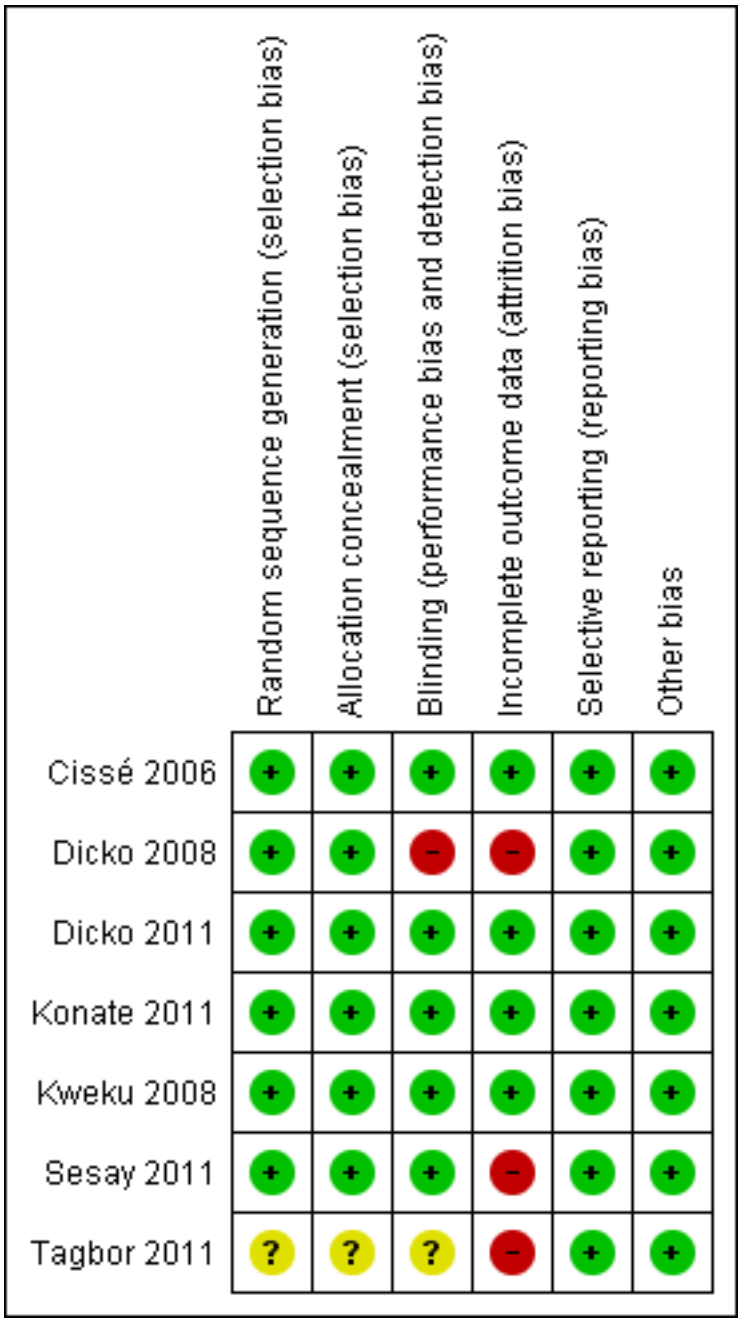
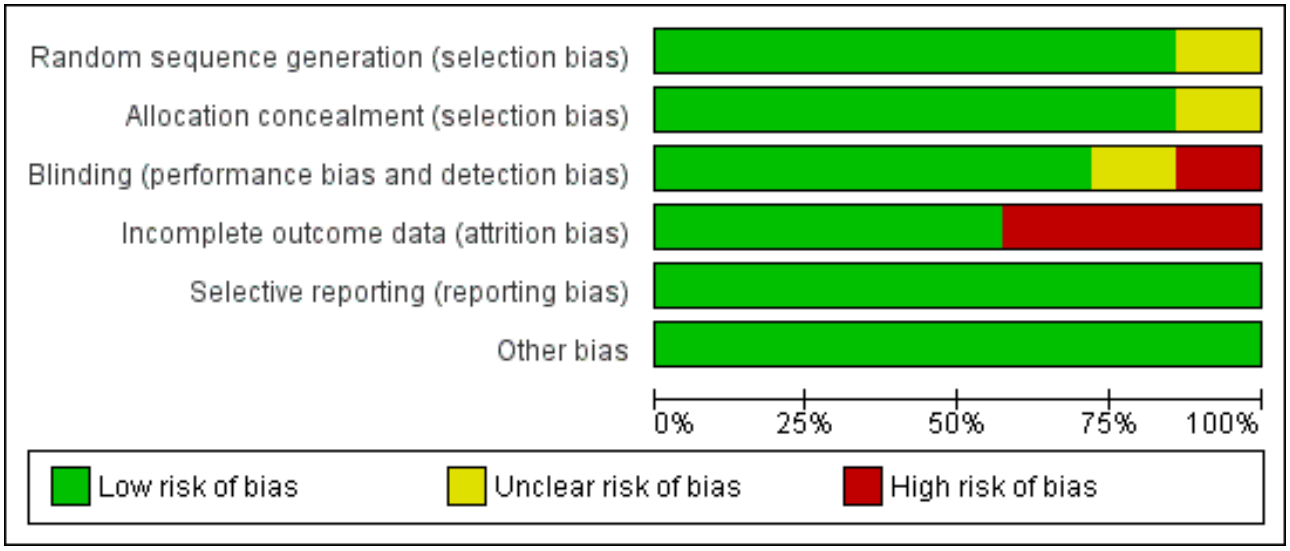


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Six trials used suitable methods to generate the allocation sequence and were classified as low risk of bias. Four used a computer; one trial was randomized in permuted blocks of 10 by a statistician (Konate 2011), while another (Kweku 2008) used simple balloting with tokens. One trial did not describe the procedure used (Tagbor 2011) and was of unclear risk.

Allocation was adequately concealed in six trials that used identical and centrally-coded drugs and placebo or sealed, opaque envelopes. Allocation concealment was unclear in one trial (Tagbor 2011.

Blinding

Five trials blinded participants and care providers/assessors. Blinding was unclear in one trial (Tagbor 2011), and not used in another described as open-label (Dicko 2008).

Incomplete outcome data

Four trials included more than 90% of randomized participants in the analysis and were classified as low risk of bias.

Three trials (Dicko 2008; Sesay 2011; Tagbor 2011) had greater than 10% attrition and were classified as high risk of bias.

Selective reporting

All seven trials were judged to be at low risk of selective reporting.

Other potential sources of bias

The six trials that randomized individuals (Cissé 2006; Dicko 2008; Dicko 2011; Konate 2011; Kweku 2008; Sesay 2011) were judged to be free of other sources of bias and thus low risk of bias.

The cluster randomized trial (Tagbor 2011) adjusted for clustering in the analysis (low risk of bias), had reasonably comparable treatment groups at baseline (low risk of bias); did not appear to be biased in terms of the recruited patients (low risk of bias); and showed no obvious differences with the trials that randomized individuals (low risk of bias).

Effects of interventions

See: **Summary of findings for the main comparison**

Three trials compared IPTc versus placebo (Cissé 2006; Dicko 2008; Kweku 2008).Two trials compared IPTc plus distribution and promotion of ITNs versus ITNs alone (Dicko 2011; Konate 2011); and two trials compared IPTc plus Home-based Manaegement of malaria (HMM) versus HMM alone (Tagbor 2011; Sesay 2011). The cluster randomized trial (Tagbor 2011) adjusted for clustering.

Clinical malaria

Overall, IPTc prevented around three-quarters of clinical malaria episodes during the intervention period (rate ratio 0.26, 95% CI 0.17 to 0.38; 9321 participants, six trials; Analysis 1.1). The size of this effect varied from a 45% reduction in Mali (Dicko 2008) to an 86% reduction in Senegal (Cissé 2006). This variation could be explained by differences in efficacy between the antimalarial regimen used, by variation in local transmission or resistance patterns, or other factors related to the conduct of the trials. However there were insufficient trials to make meaningful conclusions from subgroup analyses exploring the effects of these factors (Analysis 2.1; Analysis 3.1).

Three studies continued to monitor children for a full transmission season after IPTc was stopped. There was no observed rebound increase in malaria in children who had received the intervention compared to controls (2299 participants, three trials; Analysis 1.1).

Severe malaria

IPTc also prevented around three-quarters of severe malaria episodes (rate ratio 0.27, 95% CI 0.10 to 0.76; 5964 participants, two trials; Analysis 1.2). Two other trials [Cissé 2006, Dicko 2008] reported on severe malaria but did not provide suitable information for inclusion in the meta-analysis: Dicko 2008 reported that five cases of severe malaria occurred during the first 12 months of the

follow-up, all in the control group incidence rate of 0.048 episodes per 1000 persons-days at risk. One child in the control group of Cissé 2006 died from severe malaria.

Parasitaemia

The prevalence of parasitaemia was also reduced by IPTc compared to controls (risk ratio 0.35, 95% CI 0.25 to 0.50; 8781 participants, six trials; Analysis 1.3). Again, although all trials favoured IPTc, there was substantial heterogeneity regarding the size of the effect but too few trials to explain this heterogeneity using subgroup analyses (Analysis 2.2; Analysis 3.2).

In the post-intervention transmission season, none there was no statistically significant difference in the prevalence of parasitaemia between IPTc and controls (1627 participants, two trials; Analysis 1.3).

Death from any cause

The number of deaths observed in these trials was very low. Although fewer deaths were seen in the children who received IPTc the difference was not statistically significant (9533 participants, six trials; Analysis 1.4).

The difference in deaths was also not statistically significant in the transmission season after IPTc was stopped (1,207 participants, one trial; Analysis 1.4).

Hospital admission for any reason

No significant difference in risk of hospitalization was found between IPTc and control groups, during the intervention (7171 participants, three trials; Analysis 1.5); or post-intervention (1207 participants, one trial; Analysis 1.5).

Severe anaemia (haemoglobin < 5 g/dL)

Although the number of cases of severe anaemia reported in these trials was very low, there was a statistically significant reduction in the risk of severe anaemia with IPTc (risk ratio 0.24, 95% CI 0.06 to 0.94; 5964 participants, two trials; Analysis 1.6).

Moderately severe anaemia (haemoglobin < 8 g/dL or haematocrit < 25%)

During the intervention, there was a reduction in the risk of moderately severe anaemia in children given IPTc (risk ratio 0.71, 95% CI 0.52 to 0.98; 8805 participants, five trials; Analysis 1.7). There was substantial heterogeneity between trials, with three trials suggesting benefit and two showing almost no difference (Analysis 1.7). The cause of this heterogeneity is unclear. The trials showing greatest benefit were Dicko 2011 and Konate 2011 which both administered IPTc as amodiaquine plus sulfadoxine-pyrimethamine (Analysis 2.3; Analysis 3.3).

One cluster-randomized trial of IPTc plus HMM versus HMM (Tagbor 2011), which was not included in the meta-analysis, reported that the prevalence of severe anaemia (defined by trial authors as haemoglobin < 7 g/dL) during the intervention was 0.44% in the IPTc arm compared to 1.75% in the control arm.

Post-intervention, no difference between IPTc and control was found (768 participants, one trial; Analysis 1.7).

Any anaemia (haemoglobin < 11 g/dL)

During the intervention, the risk of mild anaemia did not significantly differ between IPTc and control groups (6786 participants, three trials; Analysis 1.8).There was heterogeneity regarding the size of the effect but again, all of the trials favoured IPTc or showed almost no difference (Analysis 1.8).

One cluster-randomized trial of IPTc plus HMM versus HMM (Tagbor 2011), which was not included in the meta-analysis, reported that the prevalence of mild anaemia (defined by trial authors as haemoglobin < 11 g/dL) during the intervention was 46.4% in the IPTc arm compared to 47.2% in the control arm.

Haemoglobin

During the intervention, three trials found no significant difference in mean haemoglobin concentration between IPTc and control arms (2266 participants, three trials; Analysis 1.9). Post-intervention, no difference between IPTc and control was found (1207 participants, one trial; Analysis 1.9).

IPTc plus co-interventions

Two trials distributed and promoted the use of ITNs to both the intervention and control groups (Dicko 2011 and Konate 2011). Despite ITN use being reported as >90% in both treatment arms, IPTc had high protective efficacy against both clinical malaria (rate ratio 0.22, 95% CI 0.13 to 0.38; 5964 participants, two trials; Analysis 2.1) and severe malaria (rate ratio 0.27, 95% CI 0.10 to 0.76; 5964 participants, two trials; Analysis 1.2).

Two trials were conducted in the context of a program of home-based management of malaria (HMM) which was provided to both the intervention and control groups (Sesay 2011; Tagbor 2011). Only Sesay 2011 reported data on clinical malaria or anaemia, and failed to show a statistically significant effect (146 participants, one trial Analysis 2.1, Analysis 2.3; Analysis 2.4). Neither trial demonstrated a statistically significant reduction in parasitaemia follwing IPTc in the presence of HMM (Analysis 2.2).

Adverse events

Serious adverse events during the intervention

All seven trials reported that there were no cases of drug-related serious adverse events.

Non-serious adverse events during the intervention

Analysis 4.1 displays adverse events reported by the three trials (Dicko 2011; Konate 2011; and Sesay 2011) that compared sulfadoxine-pyrimethamine plus amodiaquine versus a control. Children given IPTc were more likely to vomit than those in the control group (risk ratio 2.78, 95% CI 2.31 to 3.35; 3544 patients, two trials). When comparing the IPTc versus control groups, no difference in risk of diarrhoea (3951 patients, two trials), loss of appetite (3950 patients, two trials), jaundice (1353 patients, one trial), skin rash (5227 patients, three trials), itching (3949 patients, two trials), fever (3951 patients, two trials), drowsiness (2951 patients, two trials), or coughing (3913 patients, two trials), was detected.

Analysis 5.1 displays adverse events reported by Cissé 2006 that compared sulfadoxine-pyrimethamine plus artesunate versus a control. When comparing the IPTc versus control groups, there was

no difference in risk of severe skin or neurological reaction (941 patients, one trial), convulsions (942 patients, one trial), minor skin rash (945 patients, one trial), dizziness (946 patients, one trial), diarrhoea (947 patients, one trial), or vomiting after first dose (948 patients, one trial). A difference between IPTc and control was detected in terms of the risk of nervousness (risk ratio 1.39, 95% CI 1.13 to 1.70; 943 patients, one trial) and pruritus (risk ratio 3.74, 95% CI 1.06 to 13.18, 944 patients, one trial). Cissé 2006 also found that children given IPTc were more likely to vomit than those in the control group after the second (risk ratio 7.26, 95% CI 2.58 to 20.39; 949 patients, one trial) and third dose (risk ratio 13.11, 95% CI 1.73 to 99.27; 950 patients, one trial).

Data reported by Tagbor 2011, that compared sulfadoxine-pyrimethamine plus amodiaquine versus control, is presented in Table 1 but does not adjust for clustering.

Dicko 2008, that compared sulfadoxine-pyrimethamine versus control, simply reported that 'No subject was withdrawn because of allergy to sulfadoxine-pyrimethamine.'

Kweku 2008, that compared sulfadoxine-pyrimethamine plus artesunate versus control, reported that 'Adverse events were reported slightly less frequently in each of the three IPTc groups compared to the placebo group throughout the intervention period (5.6 % vs 5.9%). Diarrhoea, vomiting, drowsiness and abdominal pains were the most frequently reported symptoms in both IPTc and placebo groups. The number of children who reported at least one adverse event or any specific adverse event did not differ significantly between the study groups.' Kweku 2008 also reported that 'The incidence of mild adverse events such as fever, general weakness, vomiting, diarrhoea, abdominal pain and cough were similar in the placebo and IPTc groups'.

DISCUSSION

Summary of main results

See Summary of findings for the main comparison.

IPTc given to children in areas with seasonal malaria transmission can prevent approximately three quarters of clinical malaria episodes (*high quality evidence*), and a similar proportion of severe malaria episodes (*high quality evidence;* Appendix 2). These effects remain present even where insecticide treated net (ITN) usage is high (*high quality evidence;* Appendix 3).

IPTc probably also produces a small reduction in all-cause mortality, but the trials were underpowered to reach statistical significance (*moderate quality* evidence).

The effect on anaemia varied between studies but the risk of moderately severe anaemia is probably reduced by IPTc (*moderate quality evidence*).

Serious drug-related adverse events, if they occur, are probably rare, with none reported in the six trials (*moderate quality* evidence). Amodiaquine plus sulphadoxine-pyrimethamine is the most studied drug combination for seasonal chemoprevention. Although effective, it does cause increased vomiting in this age-group (*high quality evidence;* Appendix 5).

When antimalarial IPTc was stopped, no rebound increase in malaria was observed in the three trials which continued follow-up for one season after IPTc (Appendix 6).

Overall completeness and applicability of evidence

All seven trials included in the review were conducted in areas of West Africa where *P. falciparum* is the predominant cause of malaria and transmission is highly seasonal, and the results can reasonably be applied to other areas with similar conditions. Most studies included healthy children aged between 3 and 59 months.

Several different IPTc regimens have been proposed and evaluated and all appear effective. Amodiaquine plus sulphadoxine-pyrimethamine is the most studied with more than 50% of all trial participants, but has not been directly compared with alternative regimens.

The reduction in clinical malaria episodes was large in all the trials but with some variation in the size of this effect. The reasons for this variation are unclear, but could be due to differences in the drug regimen, or differences in the local malaria transmission or resistance patterns. The trials were too few in number to perform meaningful subgroup analyses.

The results of trials included in this review demonstrated that IPTc given to preschool children over a short period (during malaria transmission season) is unlikely to result in a rebound effect on malaria morbidity or mortality, once IPTc is stopped. While the trials that reported detailed post-intervention data are few, these results are consistent across trials and appear to support the hypothesis that IPTc, allows longer periods in between treatments for children to acquire protective malarial immunity and are therefore less likely to cause rebound morbidity and mortality than continuous prophylaxis.

Quality of the evidence

The quality of evidence has been assessed using the GRADE methodology.

The GRADE system considers ‘quality’ to be a judgment of the extent to which we can be confident that the estimates of effect are correct. The level of ‘quality’ is judged on a 4-point scale. Evidence from randomized controlled studies is initially graded as high and downgraded by one, two or three levels after full consideration of: any limitations in the design of the studies, the directness (or applicability) of the evidence, the consistency and precision of the results, and the possibility of publication bias.

The evidence that IPTc reduces clinical malaria episodes and severe malaria episodes is considered to be of 'High quality', which implies that we are confident in these estimates of effect and further research addressing these aspects is not necessary (see Summary of findings for the main comparison).

The full GRADE profiles with reasons for the downgrading of evidence quality are available as Appendices addressing 5 questions:

- Does IPTc reduce all-cause mortality and malaria morbidity in children aged < 5 years?
- Is there a rebound increase in all-cause mortality or malaria morbidity once IPTc is stopped?

- Is IPTc still effective when ITN usage is high?
- Is IPTc still effective where home-based management of malaria is practiced?
- Is amodiaquine plus sulfadoxine-pyrimethamine an effective and safe option for IPTc?

Agreements and disagreements with other studies or reviews

The findings of this review agree broadly with a similar systematic review published in 2011 (Wilson 2011), but there are some differences in the conclusions regarding an effect on mortality.

Wilson 2011 concludes that IPTc 'appears to have a substantial protective effect against all-cause mortality'. We have excluded data from some uncontrolled observational trials included by Wilson 2011, and consequently our estimates do not reach statistical significance. However, we agree that a reduction in mortality with IPTc is likely and would be consistent with the high quality evidence of a reduction in severe malaria. However, the magnitude of this reduction, appears to be around 1 averted death per 1,000 children receiving IPTc.

AUTHORS' CONCLUSIONS

Implications for practice

Giving antimalarial drugs to preschool children (age < six years) as IPTc during the malaria transmission season reduces the incidence of clinical malaria, and severe malaria. Several antimalarial drug combination options have been evaluated and show good levels of effectiveness, even in the presence of high levels of ITN use.

Implications for research

The evidence for benefit in areas with seasonal transmission is of high quality and further assessment of these antimalarials in these settings is unnecessary.

The effectiveness of IPT for pre-school age children living in settings with perennial transmission remains unclear, and may be an area for further research. However, concerns about the practicality, adverse effects, or costs of IPT in these settings may limit the usefulness of the intervention.

Concern remains about the potential for IPT to increase the development of antimalarial resistance, and resistance monitoring should be integrated into appropriate pharmaco-epidemiological studies and surveillance programmes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cissé 2006

Methods	Design: Randomized controlled trial

Cissé 2006 *(Continued)*

	Unit of randomisation: patient Length of follow up: 12 months
Participants	Number enrolled: 1088 children aged from two to 59 months Inclusion criteria: aged from two to 59 months; residence in study area Exclusion criteria: severe illness including severe anaemia
Interventions	1. Intermittent treatment: IPTi with sulfadoxine-pyrimethamine plus artesunate given once monthly Sulfadoxine-pyrimethamine (25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine) plus artesunate (4 mg/kg give once monthly for three consecutive months); 542 children 2. Placebo; 546 children All participants concurrently received routine immunization with diphtheria-pertussis-tetanus (DPT) and measles vaccines
Outcomes	1. Clinical malaria episodes 2. Anaemia 3. Hospital admissions 4. Death 5. Severe malaria 6. Adverse events 7. Sulfadoxine- pyrimethamine resistance markers
Notes	Location: Niakkhar, Senegal Malaria transmission: high/seasonal Registration number: NCT00132561 Adverse events measurement: Adverse events were monitored by three physicians. A random sample of 300 participants were visited at home within three days of being given the drug, were physically examined and their parents interviewed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Identical and centrally-coded drugs and placebo
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, care providers, and assessor were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used intention-to-treat analysis for main outcomes; accounted for 90% of trial participants in per protocol analysis.
Selective reporting (reporting bias)	Low risk	No apparent risk.
Other bias	Low risk	No apparent risk.

Dicko 2008

Methods	Design: Randomized controlled trial Unit of randomization: patient Length of follow up: 24 months
Participants	262 children aged from months to 10 years Inclusion criteria: 1) parental or other legal guardian consent; 2) aged from six months to 10 years; 3) having no chronic illness or symptomatic malaria; 4) agreeing to seek initial medical care for all medical illness in the study clinic during the entire study period; 5) having no plan to travel for a long time during the study period. Specific exclusion criteria: Children with a history of allergy to sulpha drugs or SP.
Interventions	1. Standard recommended treatment doses of SP (Fansidar®, F. Hoffman-La Roche Ltd, Basel, Switzerland) was given for IPT:1/4 tablet per 5 kg wt for age ≤12 years. All subjects were observed for at least 60 minutes for vomiting. If vomiting occurred within 30 minutes, the full dose was repeated and if it occurred within 60 minutes, 1/2 of the dose was repeated. 2. No IPT
Outcomes	Primary outcome: Incidence rate of malaria disease during intervention Secondary outcomes: Incidence rate of malaria after cessation of intervention In vivo therapeutic efficacy of SP. Severe malaria.
Notes	Location: Kambila, Mali Transmission: Seasonal and hyperendemic (parasitaemia rates 40–50% in the dry season (November – May) and 70–85% in the rainy season (June – October). Adverse events measurement: serious adverse events were monitored during the duration of the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated list of random numbers
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes used

Dicko 2008 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Described as open label
Incomplete outcome data (attrition bias) All outcomes	High risk	Atttrition rate 16.8% in the treatment arm and 15.3% in the control arm.
Selective reporting (reporting bias)	Low risk	No apparent risk.
Other bias	Low risk	No other potential risk of bias identified

Dicko 2011

Methods	Design: Randomized controlled trial Unit of randomization: patient Length of follow up: 6 months
Participants	Participants: 3017 children aged from 3 to 59 months. Inclusion criteria: Aged from 3 to 59 months at the time of enrolment Permanent residence in study area with no intention of leaving during the study period. Exclusion criteria: Presence of a severe, chronic illness, such as severe malnutrition or AIDS, history of significant adverse reaction to SP or AQ. NB: Cases of an acute illness, such as malaria, were not excluded. Such cases were treated appropriately and the child randomized and retained in the trial.
Interventions	1. IPT with Sulphadoxine Pyrimethamine (SP) and Amodiaquine (AQ) + long-lasting insecticidal nets (LLIN) SP tablets: children 5 to 9 kg: sulphadoxine 175 mg and pyrimethamine 8.75 mg per tablet children 10 to 18 kg: sulphadoxine 350 mg and pyrimethamine 17.5 mg per tablet children 19 kg or more: sulphadoxine 550 mg and pyrimethamine 26.25 mg per tablet AQ dose = 7.8 to 14 mg/kg/d: children 5 to 9 kg: 70 mg per tablet children 10 to 18 kg: 140 mg per tablet children 19 kg or more: 220 mg per tablet 2. Placebo + long-lasting insecticidal nets (LLIN): identical with treatment tablets and given in the same schedule

Dicko 2011 *(Continued)*

	Sulphadoxine Pyrimethamine (SP) SP + Amodiaquiune AQ or Placebo tablets were given during the peak malaria transmission season, with one month intervals between treatments.
Outcomes	(i) the incidence of clinical malaria (defined as "the presence of fever or a history of fever in the past 24 hours and the presence of *P. falciparum* asexual parasitaemia at any density"); (ii) incidence of severe malaria (WHO definition) (iii) malaria infection defined as the presence of asexual parasitaemia; (iv) mild, moderate, or severe anaemia defined as an haemoglobin (Hb) concentration < 11 g/dL, < 8 g/dL, and < 5 g/dL, respectively; (v) hospital admission defined as a stay of at least 24 hours in hospital for treatment; (vi) anthropometric indicators including wasting, stunting, and underweight (WHO definition) (vii) safety and tolerability measured by the occurrence of non-serious and serious adverse events.
Notes	Location: Kati District in the Savannah region of Mali Transmission: highly seasonal (80%–90% of malaria cases occur August-November) Entomological inoculation rate (EIR): 9.4 and 6.6 and 37.3 infective bites per person per season, respectively in Siby and Ouelessebougou (two localities far from any river) and 37.3 infective bites per person per season in Djoliba (located on the bank of the Niger River). Adverse events measurement: "Adverse events were monitored immediately after the administration of each course of IPTc and throughout the follow-up period."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Children were individually randomized using a computer-generated random number sequence and blocks of varying length.
Allocation concealment (selection bias)	Low risk	Treatment allocations were provided within sealed, opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo tablets used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate was 2.5% and 2.9% in control and treatment arms respectively
Selective reporting (reporting bias)	Low risk	Trial was registered; no selective reporting observed
Other bias	Low risk	None identified

Konate 2011

Methods	Design: Randomized controlled trial Unit of randomization: patient Length of follow up: 6 months

Konate 2011 *(Continued)*

Participants	Children aged from three to 59 months Inclusion criteria: • Body weight at least 5 kg • Residence in one of the study villages with no plan • Signs or symptoms of severe chronic illness • Absence of signs of severe malnutrition • Signed inform consent obtained from the caregiver Exclusion criterion: • History of sensitivity to any antimalarial drug
Interventions	1. IPT with Sulphadoxine Pyrimethamine (SP) and Amodiaquine (AQ) + long-lasting insecticidal nets (LLIN) SP tablets: children 5 to 9 kg: sulphadoxine 175 mg and pyrimethamine 8.75 mg per tablet children 10 to 18 kg: sulphadoxine 350 mg and pyrimethamine 17.5 mg per tablet children 19 kg or more: sulphadoxine 550 mg and pyrimethamine 26.25 mg per tablet AQ dose = 7.8 to 14 mg/kg/d): children 5 to 9 kg: 70 mg per tablet children 10 to 18 kg: 140 mg per tablet children 19 kg or more: 220 mg per tablet 2. Placebo + long-lasting insecticidal nets (LLIN): identical with treatment tablets and given in the same schedule Sulphadoxine Pyrimethamine (SP) SP + Amodiaquiune AQ or Placebo tablets were given in August, September, and October during the peak malaria transmission season, with one month intervals between treatments.
Outcomes	Primary outcome: Incidence of clinical malaria with *P. falciparum* asexual parasites density of at least 5000 asexual parasites of *P. falciparum* per microlitre. Secondary outcomes: (1) incidence of clinical malaria (*P. falciparum* asexual parasites at any density) (2) the incidence of severe malaria defined according to WHO criteria (3) the prevalence of anaemia at the end of malaria transmission season (anaemia = Hb < 11 g/dL, moderately severe anaemia = Hb < 8 g/dL; severe anaemia = Hb < 5 g/dL) (4) the prevalence of parasitaemia at the end of the malaria transmission season; (5) the prevalence of wasting, stunting, and underweight at the end of malaria transmission season; (6) the incidence of all-cause hospitalization
Notes	Entomological inoculation rate (EIR) was estimated to be 173 infective bites per person per year (in 2002) with a peak in September (Burkina Faso) Proportions of children that slept under LLINs was similar in the control and in the intervention

Konate 2011 *(Continued)*

	groups (92.7% versus 92.8%). Adverse events measurement: Adverse events were monitored on the day of administration of each dose and on the day after the last dose of each treatment course by trained members of the research team who were not involved in giving treatment. Questions were asked specifically about the occurrence of listed symptom/events.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization list was prepared by a statistician in three strata; treatment group was assigned in each stratum in a 1:1 ratio in permuted blocks of 10.
Allocation concealment (selection bias)	Low risk	Number sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo tablets used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate 0.7% and 0.1% in control and intervention groups respectively
Selective reporting (reporting bias)	Low risk	Trial registered, and outcomes in protocol were essentially accounted
Other bias	Low risk	None identified

Kweku 2008

Methods	Randomized controlled trial Lenght of follow up: No active follow up after six months duration of the intervention (Surveys and malaria tests done at 12months).
Participants	Number enrolled: 2451 Inclusion criteria: Children aged from two to 59 months in the selected communities; children resident in the study area and likely to be available for follow-up for six-12 months; consent by parent /guardian of child; absence of severe malnutrition, chronic diarrhoea or history of convulsions; absence of prostration, extreme weakness (inability to stand or sit) at the time of enrolment; no history of AQ, SP or AS intake within the past two weeks; absence of history of hypersensitivity to any of the study drugs. Exclusion criteria:failure to meet any of the above inclusion criteria
Interventions	1. Intermittent treatment: IPTc with artesunate plus amodiaquine (AS+AQ) monthly or every two months, or sulphadoxine-pyrimethamine (SP) every two months and placebo over a period of six months. Children aged from three to five months received a quarter of a tablet, those aged six–11 months half a tablet, those aged from 12 to 23 months three quarters of a tablet (3/4) and those aged 24 months and above received one tablet each of SP, co-formulated AS+AQ or placebo. 2. Placebo
Outcomes	1. Anaemia

Kweku 2008 *(Continued)*

	2. Severe anaemia 3. Clinical episodes of malaria 4. Hospitalizations 5. Malaria admissions (severe malaria) 6. Deaths 7. Adverse events
Notes	Location: Hohoe district, Ghana Malaria transmission:Intense with two seasonal peaks and entomological inoculation rate of 65 infective bites/person/year. Adverse events measurement: Field workers visited study children to solicit any adverse events seven to 10 days after administration of study drugs. Reported adverse events were investigated and managed by a study clinician.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple balloting with tokens representing treatment groups
Allocation concealment (selection bias)	Low risk	Centrally packed and labelled drug containers
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, care providers, and assessor were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate 5.7% to 8.3% (average 6%)
Selective reporting (reporting bias)	Low risk	Study protocol available
Other bias	Low risk	None identified

Sesay 2011

Methods	Design: Randomized controlled trial Unit of randomization: patient Length of follow up:6 months
Participants	Children aged from three to 59 months Number enrolled: 1277 (Intervention 638; Control 639) Inclusion criteria: Written informed consent from parents or guardians

Sesay 2011 *(Continued)*

	No clinically significant acute or chronic disease. Exclusion criteria Known allergy to any antimalarial drug Presence of acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal disease.
Interventions	1. IPT with Sulphadoxine Pyrimethamine (SP) and Amodiaquine (AQ) Dosage of SP (500 mg sulphadoxine/25 mg pyrimethamine) Children aged from three to 11 months: half a tablet Children aged from one to 5 years: a whole tablet Dosage of AQ (200 mg base tablets) Children aged from three to 11 months: One quarter tablet Children aged from one to 2 years: half tablet Children aged from three to five years: whole tablet 2. Placebo (same tablet dose given) All children had HMM.
Outcomes	Primary outcome: • Incidence of clinical malaria (axillary temp ≥ 37.5°C or a history of fever within the previous 48 hours accompanied by asexual malaria parasitaemia at a density of ≥5000 parasites/μL) Secondary outcomes: • Incidence of a febrile illness with parasitaemia at any density among children seen by a village health worker (VHW) or at a health centre or hospital, • Incidence of anaemia among children seen at a health centre or hospital, • Prevalence of parasitaemia at the end of malaria transmission season • Prevalence of anaemia at the end of malaria transmission season • Proportion of children who received three IPTc treatment courses • Proportion of children who received no IPTc treatment course.
Notes	Location: The Gambia Transmission: Seasonal (rainy season and immediately afterwards: July to November); peak during October and November. Entomological inoculation rate: varies across the country with reported estimates in the range of one to 177 infective bites per person per year Adverse events measurement: Passive surveillance for malaria was carried out during the 2008 transmission season. VHWs referred children who failed to improve on malaria treatment and those with danger signs (breathing difficulty, severe weakness, convulsions, severe diarrhoea or vomiting) to the nearest health facility for further evaluation and management.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated list of random numbers in blocks of 12 Unit of randomization: individual

Sesay 2011 *(Continued)*

Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo tablets identical with treatments used
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rate 16.5% in treatment group and 19.5% in control group
Selective reporting (reporting bias)	Low risk	No apparent risk.
Other bias	Low risk	None identified

Tagbor 2011

Methods	Design: Randomized controlled trial (units of randomization = communities). Unit of randomization: Community Cluster adjusted: Yes, by analysing at the cluster-level. Intra-cluster correlation coefficients: Haemoglobin (ICC 0.05) and Parasitaemia (ICC 0.04). Length of follow up: 17 months
Participants	Number enrolled: 1490 children aged between three and 59 months Number of clusters: 13 Average cluster size: 114.55 Inclusion criteria: All children were eligible for enrolment unless they were known to suffer from chronic diseases
Interventions	1. Intermittent treatment with AS+AQ every two months and HMM (six communities) 2. HMM (Seven communities) Duration of study: April 2007 to November 2008.
Outcomes	1. Parasitaemia 2.Severe anaemia 3.Adverse events
Notes	Location: Kwaso subdistrict, Ashanti Region of Ghana First dose of treatment observed by study team while 2nd and 3rd doses were given by the caregiver at home Adverse events measurement: “It was not possible to maintain comprehensive surveillance of adverse events and compliance.”“A subset of children, approximately 100 in each intervention group, were assessed for adverse events after treatment for febrile episodes.”
Risk of bias	

Tagbor 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Cluster randomized. Procedure used to generate allocation sequence not described.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding procedure described
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rate quite high (19.8% in treatment arm and 28.6% in control arm)
Selective reporting (reporting bias)	Low risk	No apparent risk.
Other bias	Low risk	Adjusted for clustering in the analysis (analysed at the cluster level); had reasonably comparable treatment groups at baseline; no apparent loss of clusters; no obvious recruitment bias; and no obvious differences with the trials that randomized individuals.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
A-Schellenberg 2010	Participants < 6 years (young infants).
Akenzua 1985	Includes participants aged more than 6 years
Allen 1990	Cross-sectional survey to determine sensitivity of *P. falciparum* after chemoprophylaxis
Alonso 1993	Chemoprophylaxis (not IPT)
Archibald 1956	Non-randomized intervention trial
Barger 2009	Randomized control trial with participants aged from six to13 years
Bell 2008	Control arm was not given placebo or no preventive intervention
Bjorkman 1985a	Non-randomized prospective study to investigate susceptibility of *P. falciparum* following a period of chemosuppression
Bjorkman 1985b	Surveys
Bjorkman 1986	Non-randomized study
Bojang 2010a	Control arm not randomized
Bojang 2010b	Only anaemic participants included

Study	Reason for exclusion
Bradley-Moore 1985	Quasi-randomized controlled trial
Chandramohan 2005	Participants < 6 years (young infants)
Charles 1961	Randomized controlled trial with participants aged from five to 14 years
Cisse 2009	No control arm (placebo or no preventive treatment)
Clarke 2008	Randomized controlled trial with participants aged from five to 18 years
Colbourne 1955	Non-randomized intervention study
Coosemans 1987	Randomized controlled trial with participants aged from six to 14 years and no group given placebo only
Coulibaly 2002	Randomized controlled trial; adults and older children included as participants
David 1997	Chemoprophylaxis (not IPT)
Delmont 1981	Mass drug administration with participants > 6 years
Desai 2003	Only anaemic participants included.
Dicko 2010	No desired outcomes measured
Escudie 1961	Not a randomized controlled trial
Fasan 1970	Randomized controlled trial with participants aged from six to 12 years
Fasan 1971	Randomized controlled trial with participants aged from five to 12 years
Fernando 2006	Randomized controlled trial of school children aged from six to 12 years
Gosling 2009	Participants < 6 years (young infants).
Greenwood 1988	Chemoprophylaxis (not IPT)
Greenwood 1989	Chemoprophylaxis (not IPT)
Greenwood 1995	Chemoprophylaxis (not IPT)
Grobusch 2007	Participants < 6 years (young infants).
Harland 1975	Longitudinal observational study
Hogh 1993	Chemoprophylaxis (not IPT)
Hogh 1994	Randomized controlled trial with participants aged from seven to 12 years
Karunakaran 1980	Included patients aged over 6 years (0-20+ years)
Karwacki 1990	Two randomized controlled trials with participants aged from six to 15 years
Kobbe 2007	Participants < 6 years (young infants).

Study	Reason for exclusion
Kollaritsch 1988	Included patients aged 9-60 years
Kweku 2009	No control arm (placebo or no preventive antimalarial treatment). Both study arms received same antimalarial regimen for IPTc.
Laing ABG 1970	Non-randomized controlled trial
Lell 1998	Randomized controlled trial with participants aged from four to 16 years
Lell 2000	Randomized controlled trial with participants aged from 12 to 20 years
Lemnge 1997	Chemoprophylaxis (not IPT)
Lewis 1975	Not randomized controlled trial
Limsomwong 1988	Randomized controlled trial with participants aged from five to 16 years
Lucas 1969	Randomized controlled trial with participants aged from eight to 17 years
Lwin 1997	Participants of all ages
MacCormack 1983	Malaria suppression project with chloroquine (not a randomized controlled trial)
Macete 2006	Participants < 6 years (young infants).
Massaga 2003	Participants < 6 years (young infants).
McGregor 1966	Randomized controlled trial with both children and adult participants
Menendez 1997	Chemoprophylaxis (not IPT)
Menon 1990	Chemoprophylaxis (not IPT)
Miller 1954	Not randomized controlled trial
Mockenhaupt 2007	Participants < 6 years (young infants).
Murphy 1993	Chemoprophylaxis for *P. vivax* malaria (not a randomized controlled trial)
Nahum 2007	Control arm was not given placebo or no preventive intervention
Nakibuuka 2009	Randomized controlled trial with participants aged from six months to 12 years Control arm was not given placebo or no preventive intervention
Nevill 1988	Randomized controlled trial with participants aged from six to 18 years
Nevill 1994	Randomized controlled trial with participants aged from eight to nine years
Nsimba 2008	Control arm was not given placebo or no preventive intervention
Nwokolo 2001	Randomized controlled trial with both children and adult participants
Odhiambo 2010	Participants < 6 years (young infants).

Study	Reason for exclusion
Onori 1982	Seroepidemiological survey to determine whether chloroquinized salt affected immunity to malaria.
Otoo 1988a	Chemoprophylaxis (not IPT)
Oyediran 1993	Quasi-randomized (alternate allocation) of preschool children
Pang 1989	Randomized controlled trial with participants aged from six to 15 years
Panton 1985	Drug sensitivity survey
Pividal 1992	Randomized controlled trial with participants aged from seven to 12 years
Pribadi 1986	Chemoprophylaxis given to all villagers (including adults)
Pringle 1966	Observational study following chemoprophylaxis to document early course of untreated *P. falciparum* malaria in semi-immune children
Ringwald 1989	Randomized controlled trial with adult participants
Robert 1989	Prospective non-randomized study
Rohner 2010	Randomized controlled trial with participants aged from six to 14 years Control arm was not given placebo or no preventive intervention
Rooth 1991	Randomized controlled trial with participants aged from six to 14 years
Rosen 2005	Not randomized controlled trial
Saarinen 1988	Not randomized controlled trial
Schapira 1988	Randomized controlled trial with participants aged from seven to 14 years
Schellenberg 2001	Randomized controlled trial of mostly infants (IPTi)
Schellenberg 2004	Open-label randomized controlled trial of participants aged from two months to four years in which sulfadoxine-pyrimethamine was given to both the control group (one dose) and intervention group (three doses at monthly intervals)
Schellenberg 2005	Participants < 6 years (young infants).
Schneider 1962	Randomized trial in which the control group received a different antimalarial and not placebo
Sokhna 2008	Control arm was not given placebo or no preventive intervention
Stace 1981	Not randomized controlled trial
Sukwa 1999	Randomized controlled trial with adult participants
Thera 2005	Randomized controlled trial with participants aged from five to 15 years
Verhoef 2002	Only anaemic participants included.
von Seidlein 2003	Adults and children > 6 years included as participants

Study	Reason for exclusion
Vrbova 1992	Randomized controlled trial with participants aged from seven to 14 years
Watkins 1987	Randomized controlled trial with participants aged from six to 10 years
Weiss 1995	Randomized controlled trial with participants aged from nine to 14 years
Win 1985	Randomized controlled trial with adult participants aged 18 to 40 years
Wolde 1994	Chemoprophylaxis (not IPT)

DATA AND ANALYSES

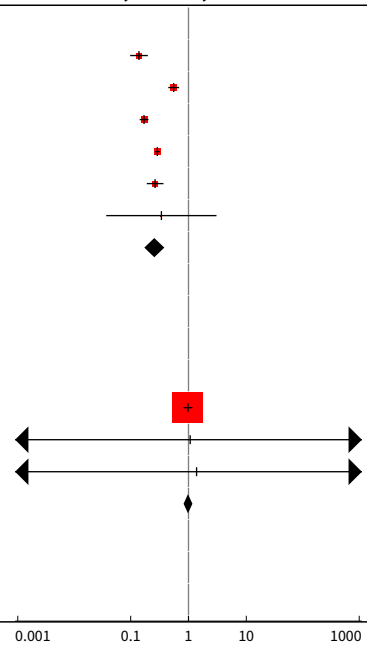
Comparison 1. IPTc versus placebo or no IPTc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical malaria	6		Rate Ratio (Random, 95% CI)	Subtotals only
1.1 During intervention	6	9321	Rate Ratio (Random, 95% CI)	0.26 [0.17, 0.38]
1.2 Post-intervention	3	2299	Rate Ratio (Random, 95% CI)	0.98 [0.82, 1.17]
2 Severe malaria	2		Rate Ratio (Fixed, 95% CI)	Subtotals only
2.1 During intervention	2	5964	Rate Ratio (Fixed, 95% CI)	0.27 [0.10, 0.76]
2.2 Post-intervention	0	0	Rate Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Parasitaemia	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 During intervention	5	8781	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.25, 0.50]
3.2 Post-intervention	2	1627	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.89, 1.16]
4 Death from any cause	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 During intervention	6	9533	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.31, 1.39]
4.2 Post-intervention	1	1207	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.39, 2.73]
5 Hospital admission for any reason	3		Rate Ratio (Fixed, 95% CI)	Subtotals only
5.1 During intervention	3	7171	Rate Ratio (Fixed, 95% CI)	0.66 [0.41, 1.05]
5.2 Post-intervention	1	1207	Rate Ratio (Fixed, 95% CI)	1.13 [0.00, 770.22]
6 Severe anaemia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 During intervention	2	5964	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.06, 0.94]

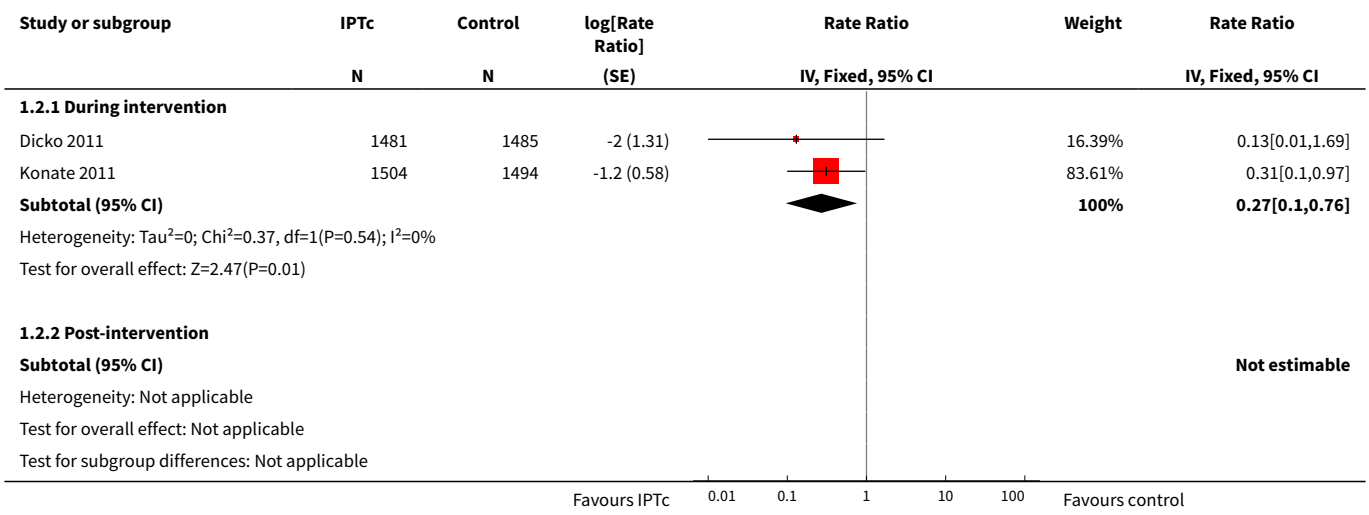
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Moderately severe anaemia	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 During intervention	5	8805	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.52, 0.98]
7.2 Post-intervention	1	768	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.53, 1.20]
8 Any anaemia	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 During intervention	3	6786	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.65, 1.04]
9 Haemoglobin	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 During intervention	3	2266	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.08, 0.14]
9.2 Post-intervention	1	1207	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.24, 0.30]

Analysis 1.1. Comparison 1 IPTc versus placebo or no IPTc, Outcome 1 Clinical malaria.

Study or subgroup	IPTc N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
1.1.1 During intervention						
Cissé 2006	435	437	-2 (0.18)		18.06%	0.14[0.1,0.2]
Dicko 2008	116	116	-0.6 (0.11)		19.8%	0.55[0.45,0.69]
Dicko 2011	1481	1485	-1.8 (0.09)		20.18%	0.17[0.14,0.2]
Konate 2011	1504	1494	-1.2 (0.05)		20.74%	0.29[0.26,0.32]
Kweku 2008	594	613	-1.3 (0.17)		18.34%	0.26[0.19,0.37]
Sesay 2011	513	533	-1.1 (1.12)		2.88%	0.34[0.04,3.05]
Subtotal (95% CI)					**100%**	**0.26[0.17,0.38]**
Heterogeneity: Tau²=0.2; Chi²=84.28, df=5(P<0.0001); I²=94.07%						
Test for overall effect: Z=6.66(P<0.0001)						
1.1.2 Post-intervention						
Cissé 2006	435	437	-0 (0.09)		99.98%	0.98[0.82,1.17]
Dicko 2008	109	111	0.1 (15.75)		0%	1.07[0,2.734166257630583E13]
Kweku 2008	594	613	0.3 (6.78)		0.02%	1.38[0,813056.45]
Subtotal (95% CI)					**100%**	**0.98[0.82,1.17]**
Heterogeneity: Tau²=0; Chi²=0, df=2(P=1); I²=0%						
Test for overall effect: Z=0.22(P=0.82)						
Test for subgroup differences: Chi²=36.1, df=1 (P<0.0001), I²=97.23%						

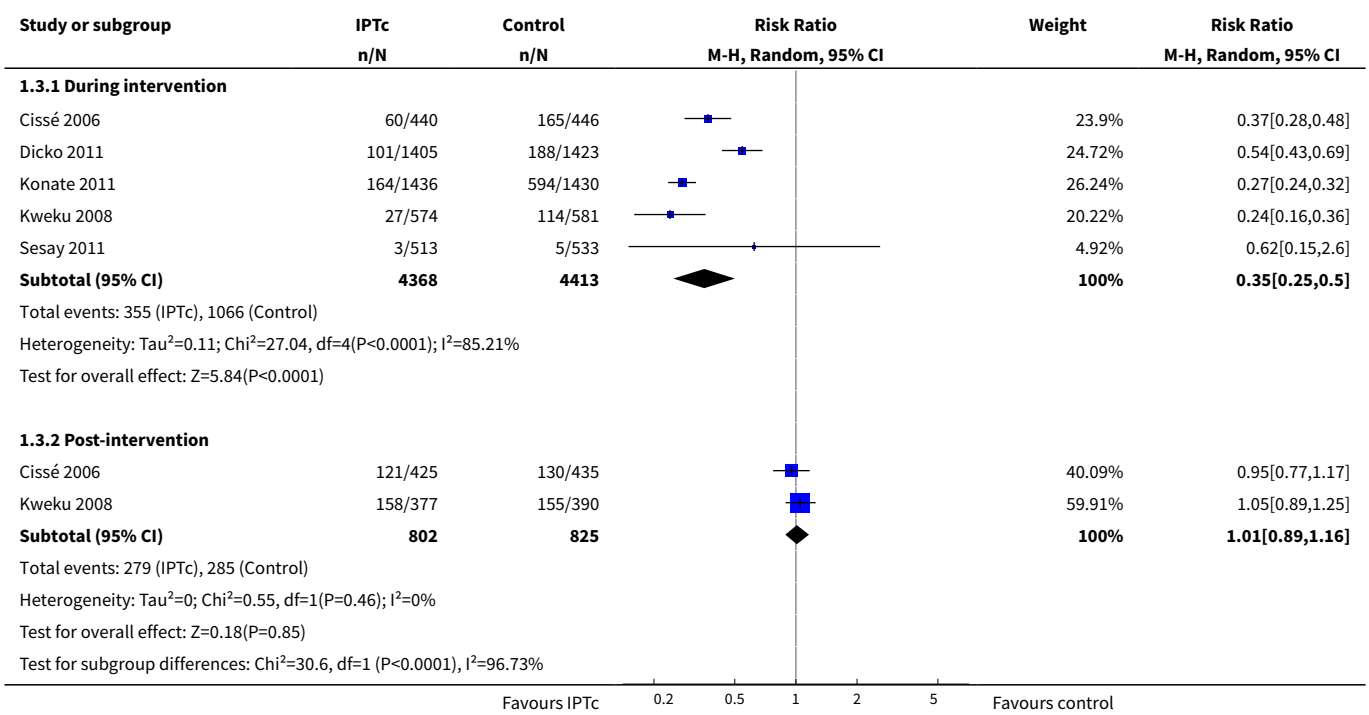


Analysis 1.2. Comparison 1 IPTc versus placebo or no IPTc, Outcome 2 Severe malaria.



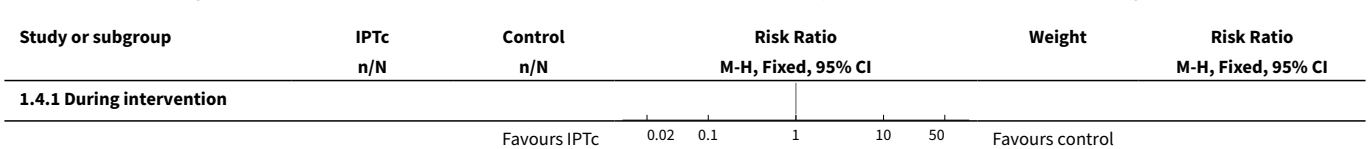
Study or subgroup	IPTc N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Fixed, 95% CI	Weight	Rate Ratio IV, Fixed, 95% CI
1.2.1 During intervention						
Dicko 2011	1481	1485	-2 (1.31)		16.39%	0.13[0.01,1.69]
Konate 2011	1504	1494	-1.2 (0.58)		83.61%	0.31[0.1,0.97]
Subtotal (95% CI)					**100%**	**0.27[0.1,0.76]**
Heterogeneity: Tau²=0; Chi²=0.37, df=1(P=0.54); I²=0%						
Test for overall effect: Z=2.47(P=0.01)						
1.2.2 Post-intervention						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

Analysis 1.3. Comparison 1 IPTc versus placebo or no IPTc, Outcome 3 Parasitaemia.

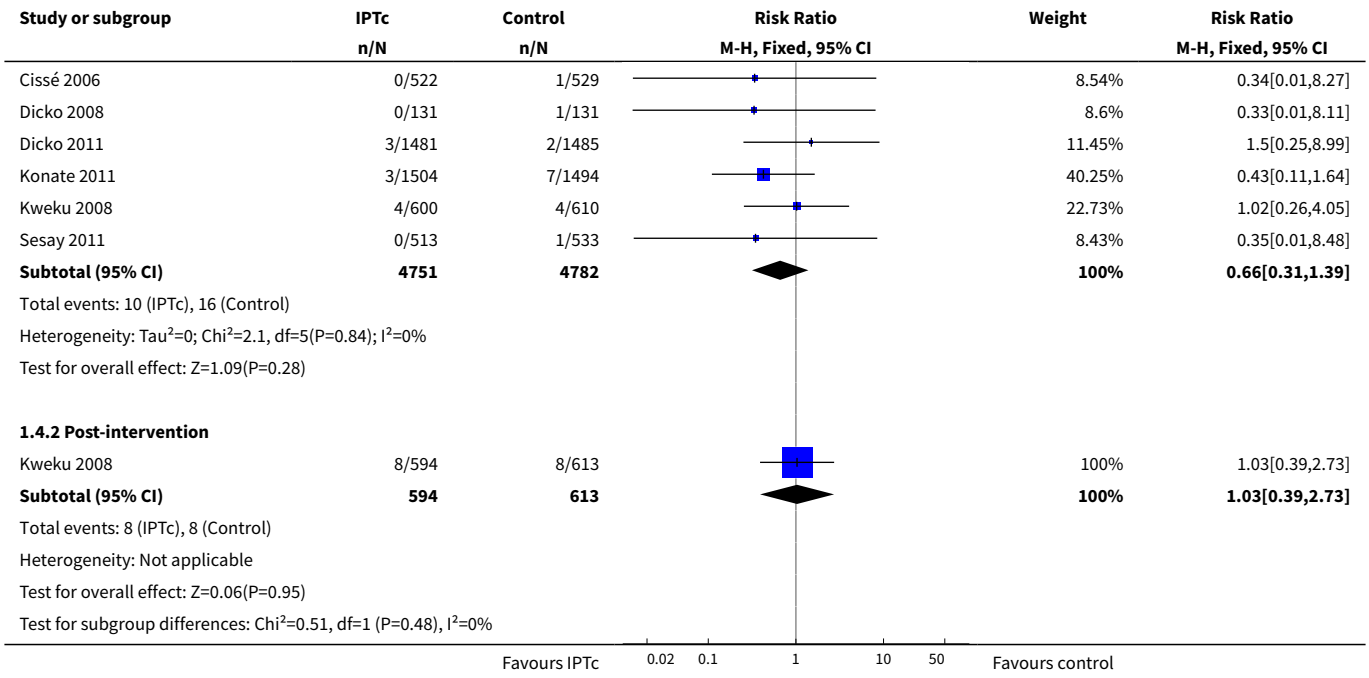


Study or subgroup	IPTc n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 During intervention					
Cissé 2006	60/440	165/446		23.9%	0.37[0.28,0.48]
Dicko 2011	101/1405	188/1423		24.72%	0.54[0.43,0.69]
Konate 2011	164/1436	594/1430		26.24%	0.27[0.24,0.32]
Kweku 2008	27/574	114/581		20.22%	0.24[0.16,0.36]
Sesay 2011	3/513	5/533		4.92%	0.62[0.15,2.6]
Subtotal (95% CI)	**4368**	**4413**		**100%**	**0.35[0.25,0.5]**
Total events: 355 (IPTc), 1066 (Control)					
Heterogeneity: Tau²=0.11; Chi²=27.04, df=4(P<0.0001); I²=85.21%					
Test for overall effect: Z=5.84(P<0.0001)					
1.3.2 Post-intervention					
Cissé 2006	121/425	130/435		40.09%	0.95[0.77,1.17]
Kweku 2008	158/377	155/390		59.91%	1.05[0.89,1.25]
Subtotal (95% CI)	**802**	**825**		**100%**	**1.01[0.89,1.16]**
Total events: 279 (IPTc), 285 (Control)					
Heterogeneity: Tau²=0; Chi²=0.55, df=1(P=0.46); I²=0%					
Test for overall effect: Z=0.18(P=0.85)					
Test for subgroup differences: Chi²=30.6, df=1 (P<0.0001), I²=96.73%					

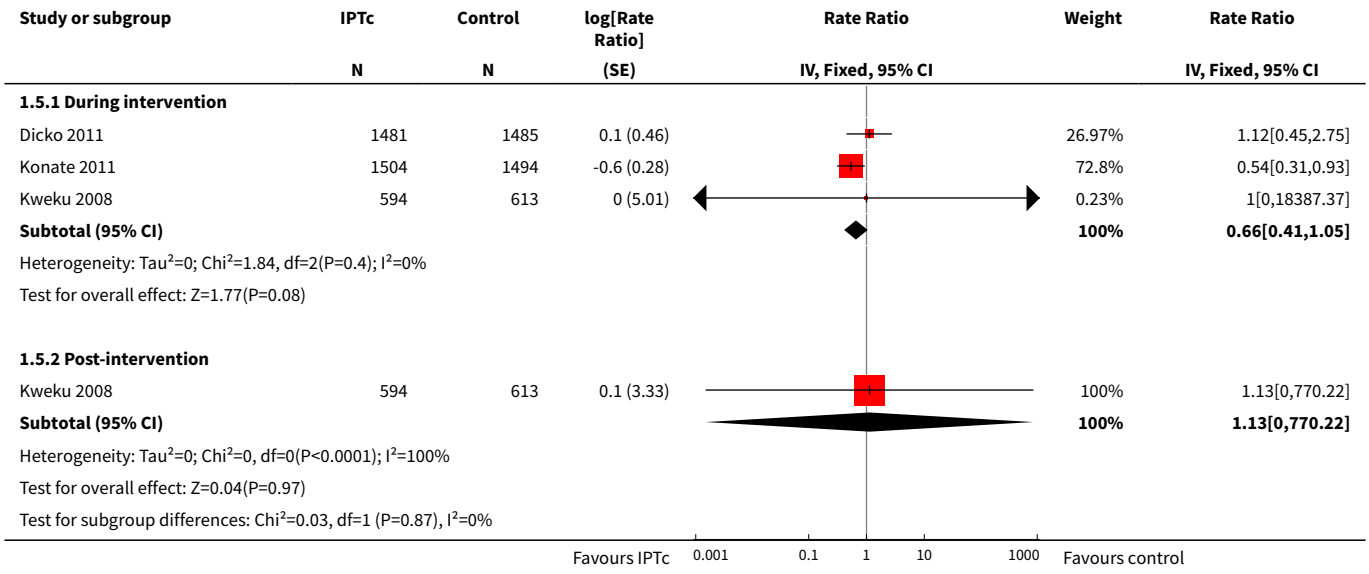
Analysis 1.4. Comparison 1 IPTc versus placebo or no IPTc, Outcome 4 Death from any cause.



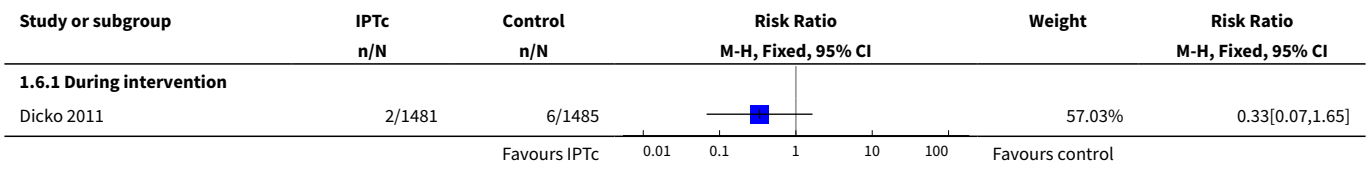
Study or subgroup	IPTc n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 During intervention					

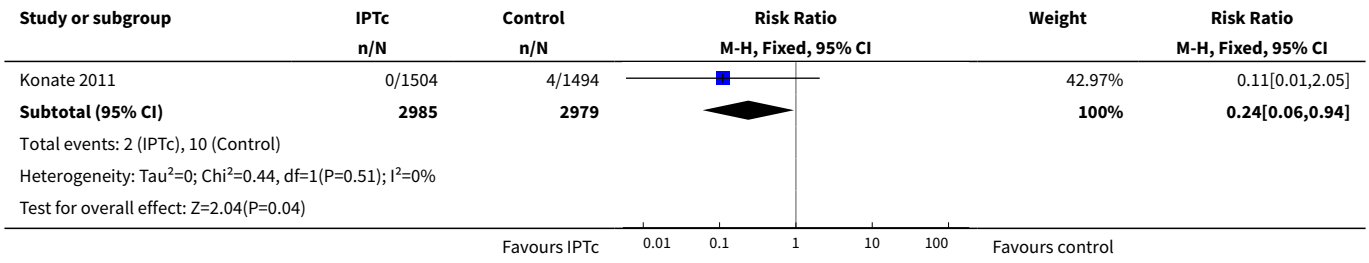


Analysis 1.5. Comparison 1 IPTc versus placebo or no IPTc, Outcome 5 Hospital admission for any reason.

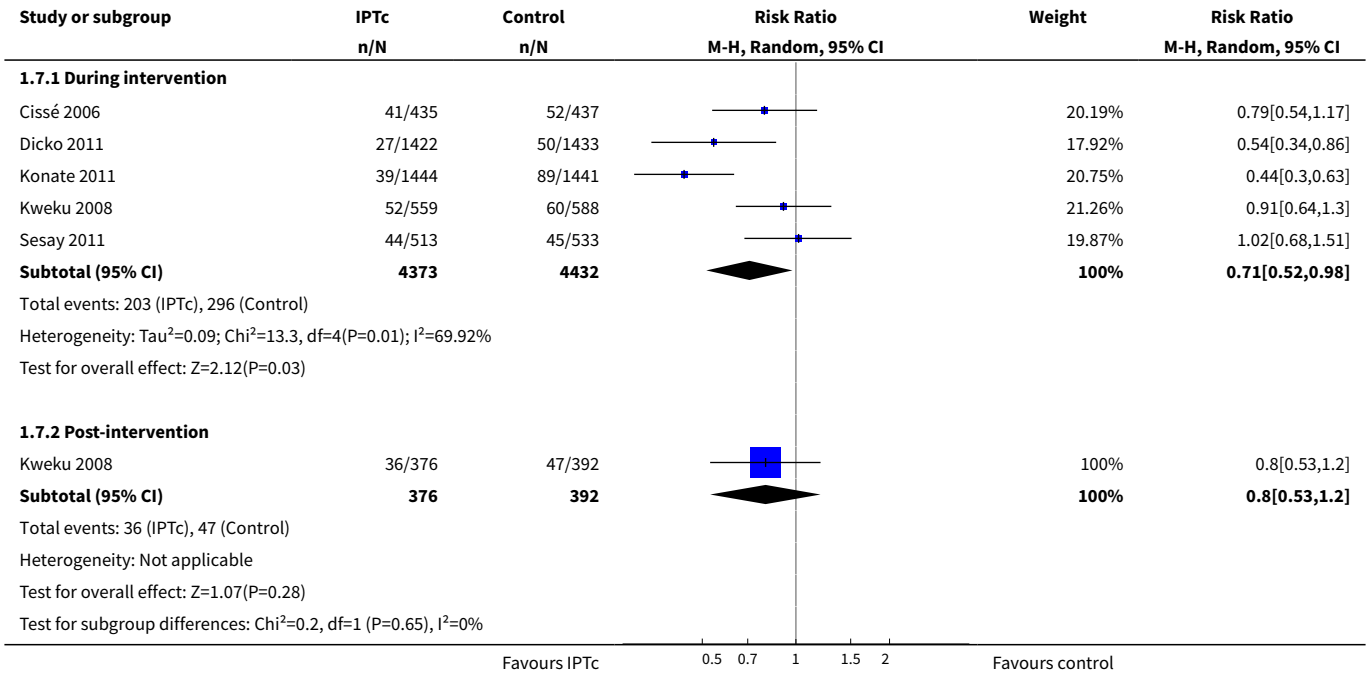


Analysis 1.6. Comparison 1 IPTc versus placebo or no IPTc, Outcome 6 Severe anaemia.

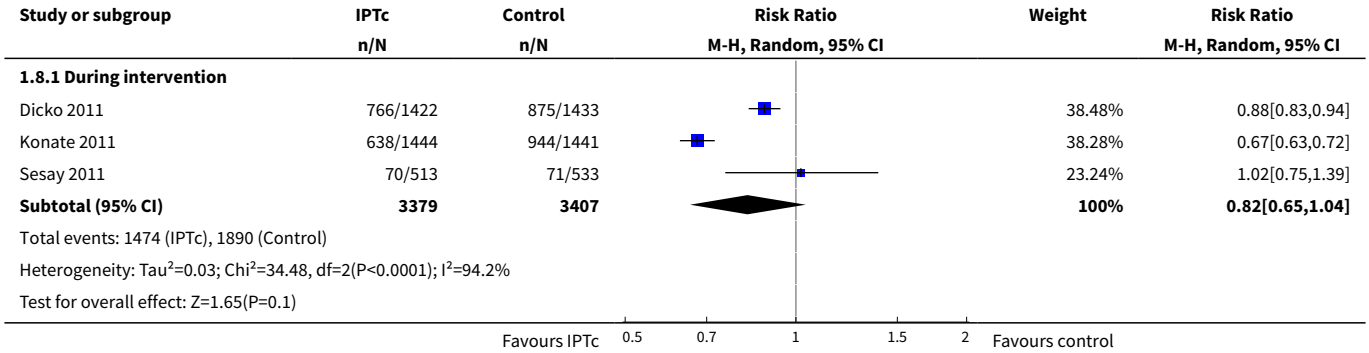




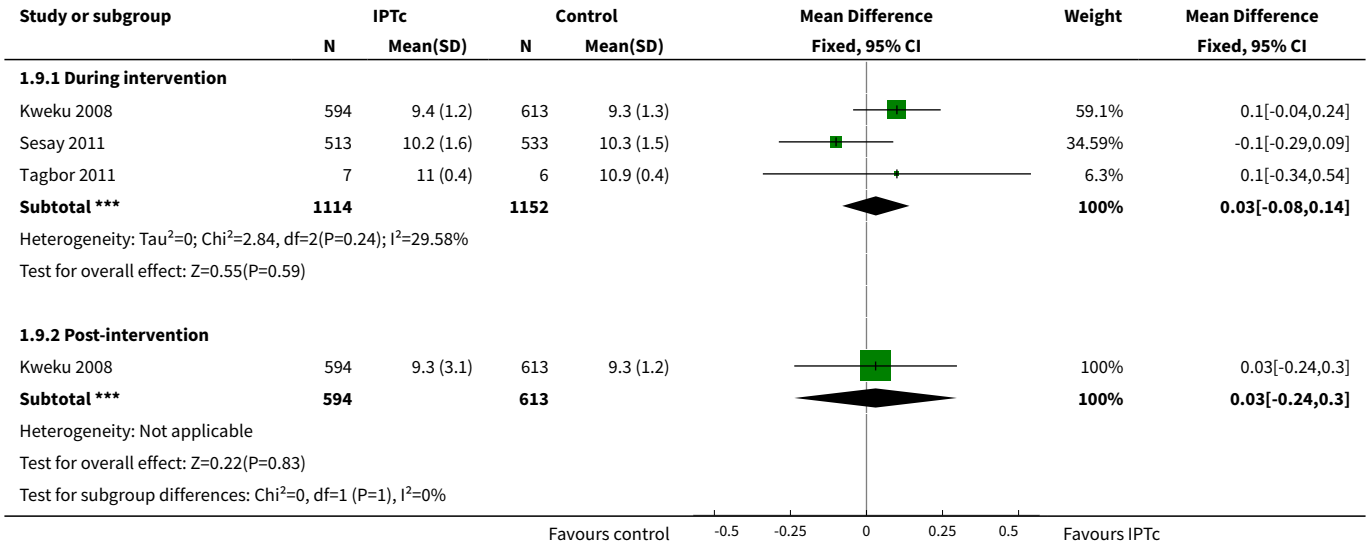
Analysis 1.7. Comparison 1 IPTc versus placebo or no IPTc, Outcome 7 Moderately severe anaemia.



Analysis 1.8. Comparison 1 IPTc versus placebo or no IPTc, Outcome 8 Any anaemia.



Analysis 1.9. Comparison 1 IPTc versus placebo or no IPTc, Outcome 9 Haemoglobin.



Comparison 2. IPTc versus placebo or no IPTc (subgroup analysis: additional interventions)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Clinical malaria	6		Rate Ratio (Random, 95% CI)	Subtotals only
1.1 During intervention (no additional)	3	2311	Rate Ratio (Random, 95% CI)	0.28 [0.12, 0.63]
1.2 During intervention (ITN)	2	5964	Rate Ratio (Random, 95% CI)	0.22 [0.13, 0.38]
1.3 During intervention (HMM)	1	1046	Rate Ratio (Random, 95% CI)	0.34 [0.04, 3.05]
2 Parasitaemia	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 During intervention (no additional)	2	2041	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.20, 0.47]
2.2 During intervention (ITN)	2	5694	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.20, 0.75]
2.3 During intervention (HMM)	2	1059	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.25, 1.90]
3 Moderately severe anaemia	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 During intervention (no additional)	2	2019	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.66, 1.11]
3.2 During intervention (ITN)	2	5740	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.36, 0.63]
3.3 During intervention (HMM)	1	1046	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.68, 1.51]

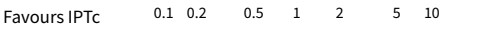
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4 Any anaemia	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 During intervention (ITN)	2	5740	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.59, 1.00]
4.2 During intervention (HMM)	1	1046	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.75, 1.39]

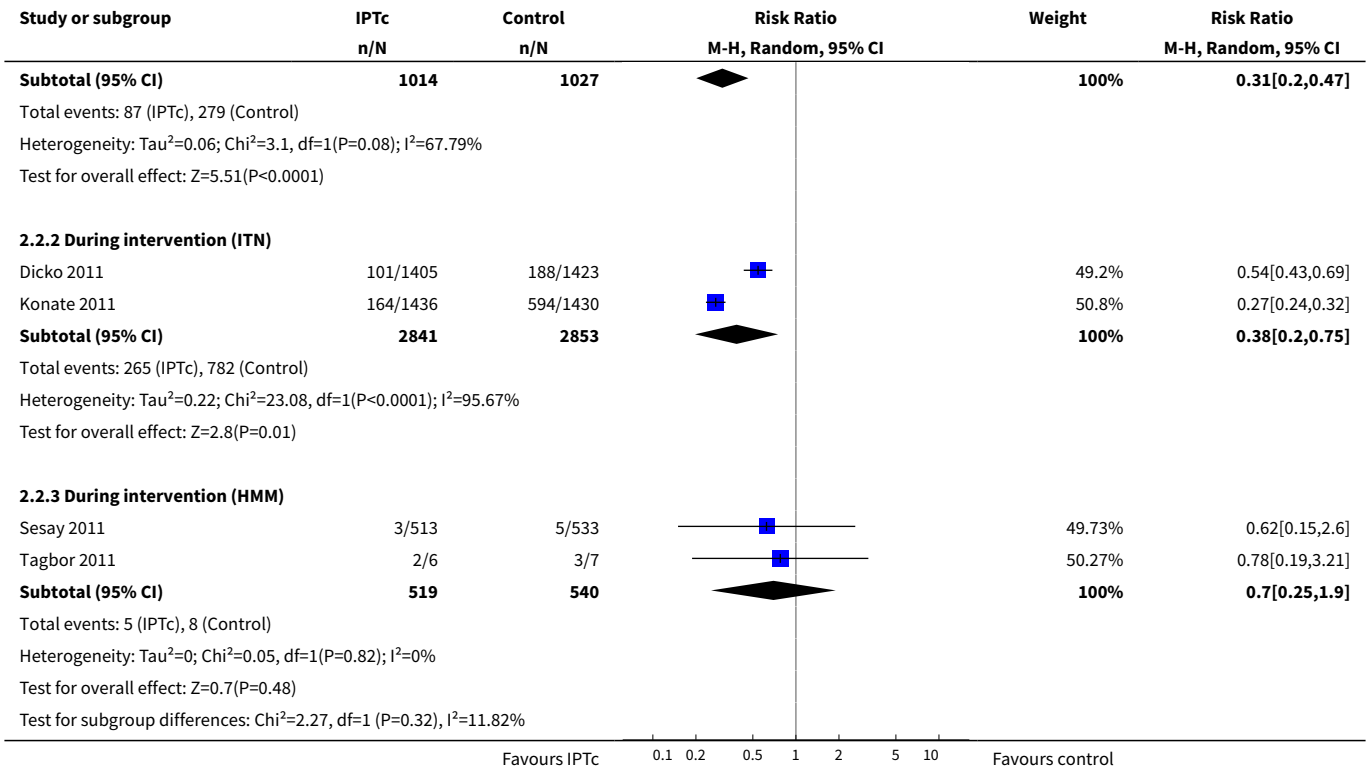
Analysis 2.1. Comparison 2 IPTc versus placebo or no IPTc (subgroup analysis: additional interventions), Outcome 1 Clinical malaria.

Study or subgroup	IPTc N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
2.1.1 During intervention (no additional)						
Cissé 2006	435	437	-2 (0.18)		32.83%	0.14[0.1,0.2]
Dicko 2008	116	116	-0.6 (0.11)		34.12%	0.55[0.45,0.69]
Kweku 2008	594	613	-1.3 (0.17)		33.05%	0.26[0.19,0.37]
Subtotal (95% CI)					**100%**	**0.28[0.12,0.63]**
Heterogeneity: Tau^2=0.51; Chi^2=46.32, df=2(P<0.0001); I^2=95.68%						
Test for overall effect: Z=3.06(P=0)						
2.1.2 During intervention (ITN)						
Dicko 2011	1481	1485	-1.8 (0.09)		49%	0.17[0.14,0.2]
Konate 2011	1504	1494	-1.2 (0.05)		51%	0.29[0.26,0.32]
Subtotal (95% CI)					**100%**	**0.22[0.13,0.38]**
Heterogeneity: Tau^2=0.14; Chi^2=26.5, df=1(P<0.0001); I^2=96.23%						
Test for overall effect: Z=5.66(P<0.0001)						
2.1.3 During intervention (HMM)						
Sesay 2011	513	533	-1.1 (1.12)		100%	0.34[0.04,3.05]
Subtotal (95% CI)					**100%**	**0.34[0.04,3.05]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.96(P=0.33)						
Test for subgroup differences: Chi^2=0.28, df=1 (P=0.87), I^2=0%						

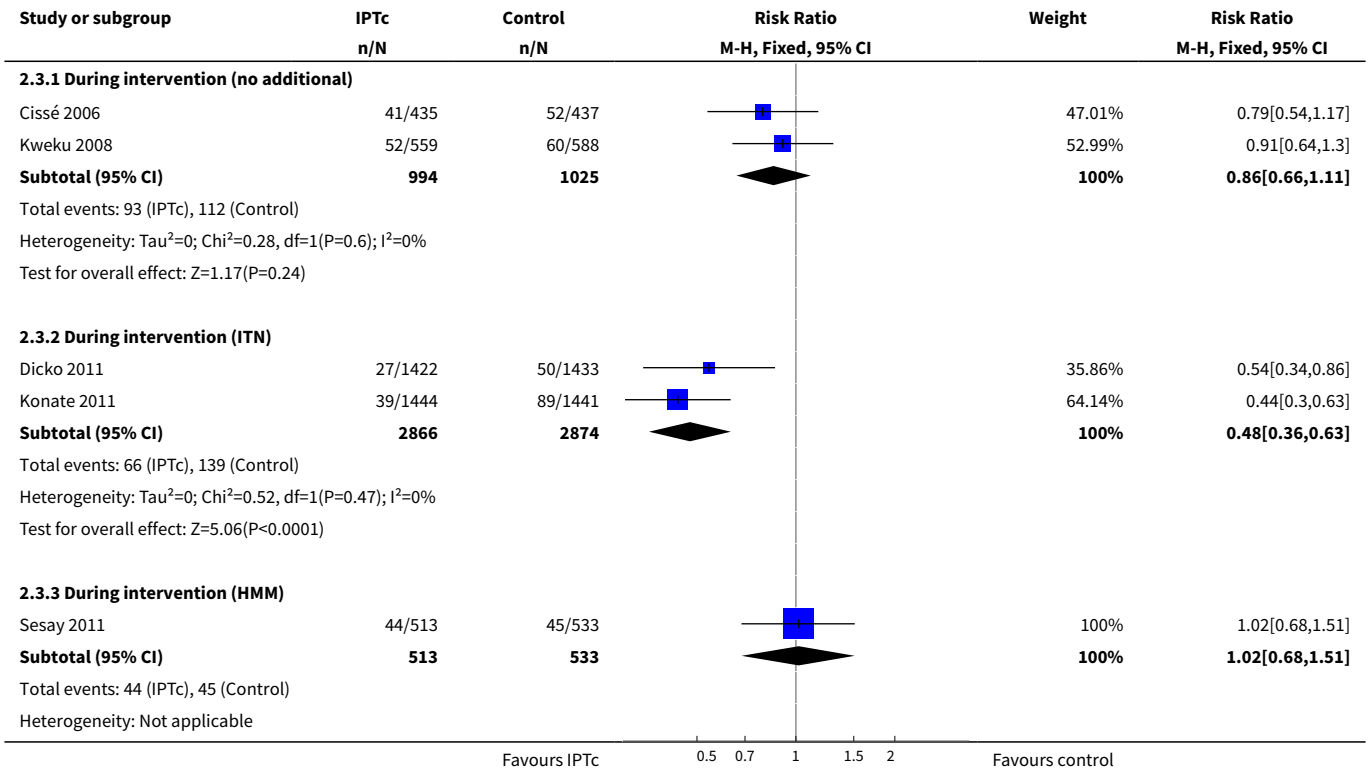
Analysis 2.2. Comparison 2 IPTc versus placebo or no IPTc (subgroup analysis: additional interventions), Outcome 2 Parasitaemia.

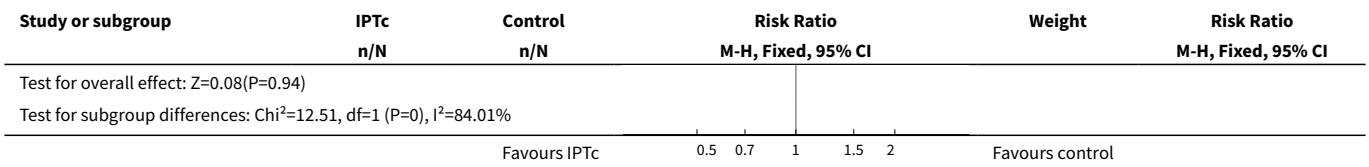
Study or subgroup	IPTc n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 During intervention (no additional)					
Cissé 2006	60/440	165/446		56.42%	0.37[0.28,0.48]
Kweku 2008	27/574	114/581		43.58%	0.24[0.16,0.36]



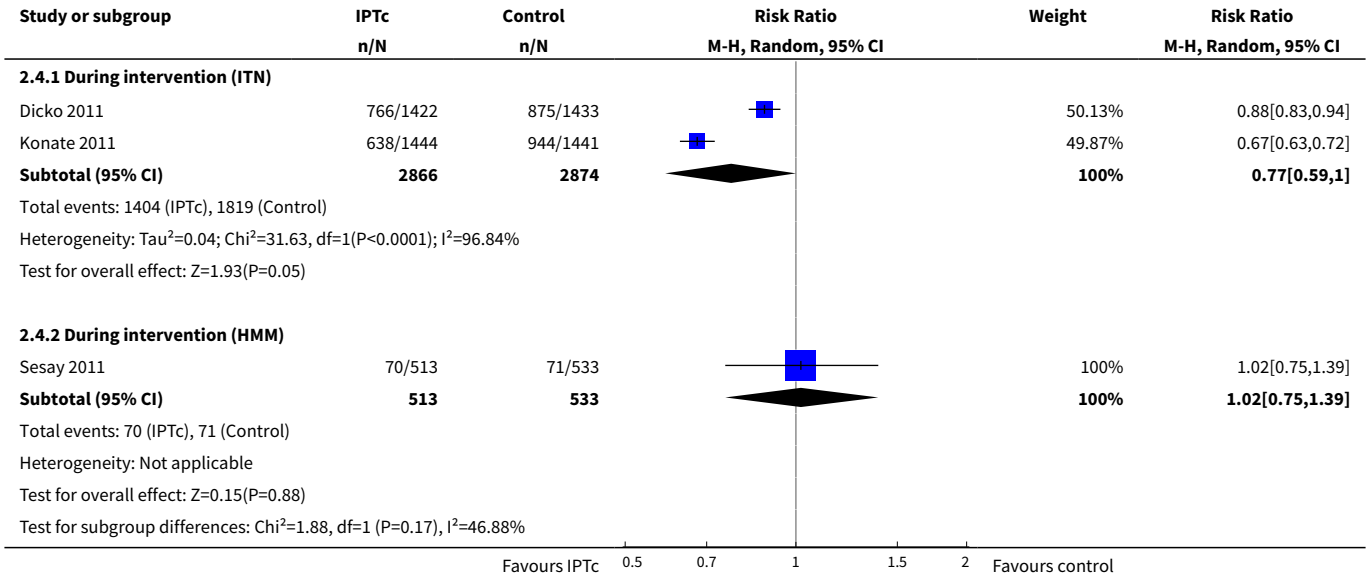


Analysis 2.3. Comparison 2 IPTc versus placebo or no IPTc (subgroup analysis: additional interventions), Outcome 3 Moderately severe anaemia.





Analysis 2.4. Comparison 2 IPTc versus placebo or no IPTc (subgroup analysis: additional interventions), Outcome 4 Any anaemia.



Comparison 3. IPTc versus placebo or no IPTc (subgroup analysis: type of antimalarial drug)

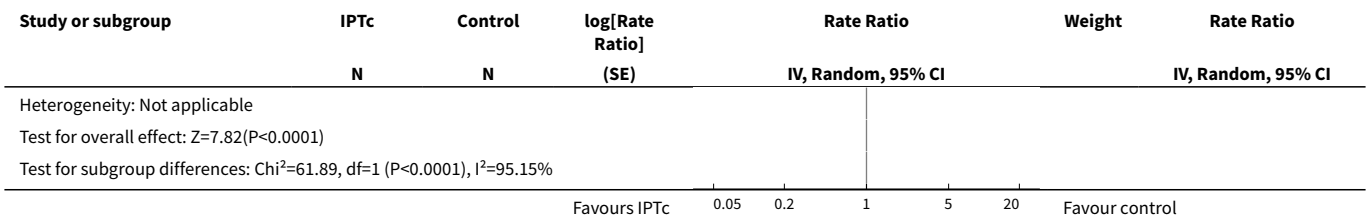
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Clinical malaria	6		Rate Ratio (Random, 95% CI)	Subtotals only
1.1 During intervention (SP)	2	1407	Rate Ratio (Random, 95% CI)	0.61 [0.50, 0.74]
1.2 During intervention (SP+AQ)	3	7010	Rate Ratio (Random, 95% CI)	0.23 [0.14, 0.37]
1.3 During intervention (SP+AS)	1	872	Rate Ratio (Random, 95% CI)	0.14 [0.10, 0.20]
1.4 During intervention (AQ+AS)	1	1207	Rate Ratio (Random, 95% CI)	0.26 [0.19, 0.37]
2 Parasitaemia	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 During intervention (SP)	1	1121	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.65, 1.07]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.2 During intervention (SP+AQ)	3	6740	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.22, 0.75]
2.3 During intervention (SP+AS)	1	886	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.28, 0.48]
2.4 During intervention (AQ+AS)	2	1168	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.12, 1.05]
3 Moderately severe anaemia	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 During intervention (SP)	1	1140	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.88, 1.70]
3.2 During intervention (SP+AQ)	2	5740	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.36, 0.63]
3.3 During intervention (SP+AS)	1	872	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.54, 1.17]
3.4 During intervention (AQ+AS)	1	1147	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.64, 1.30]

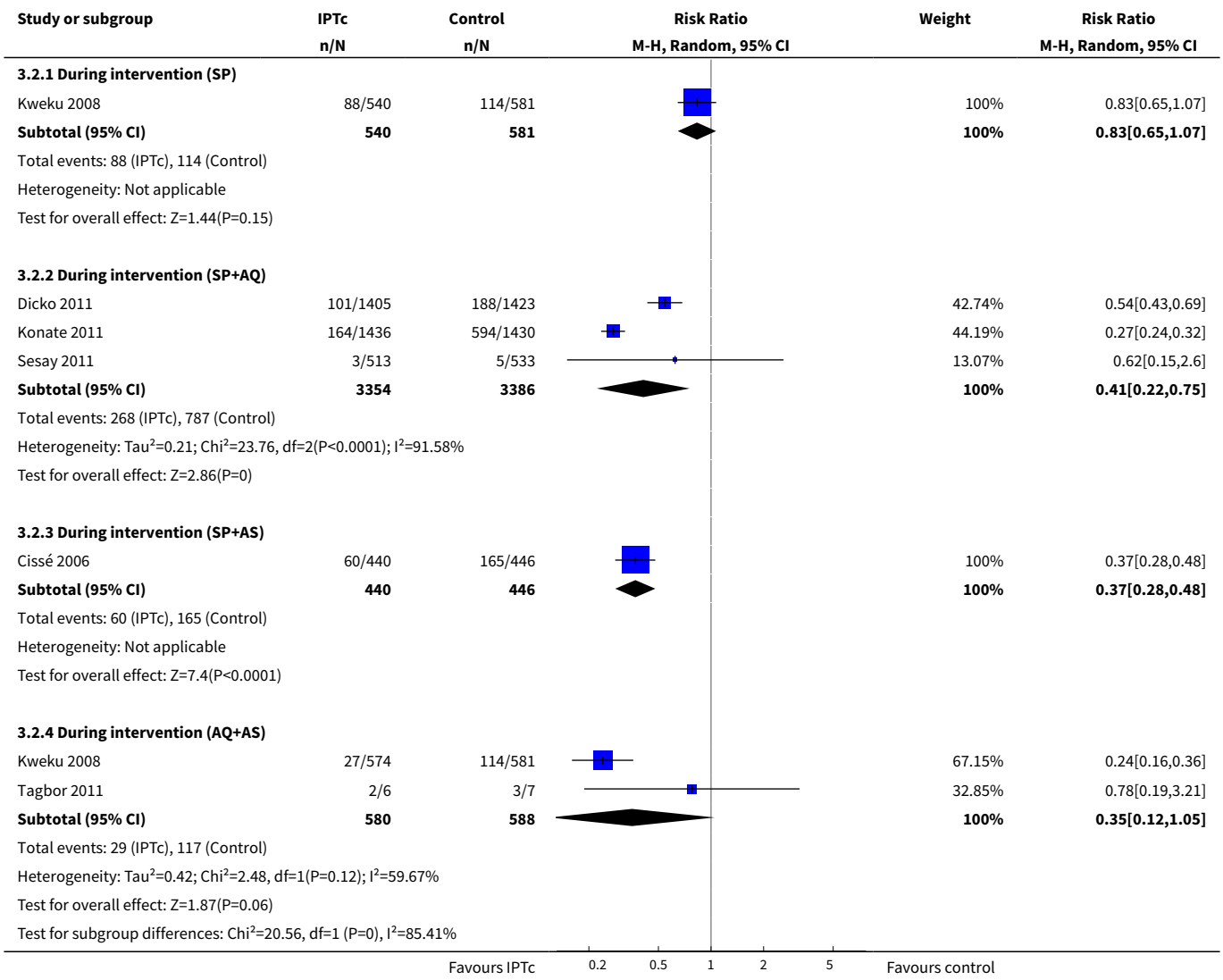
Analysis 3.1. Comparison 3 IPTc versus placebo or no IPTc (subgroup analysis: type of antimalarial drug), Outcome 1 Clinical malaria.

Study or subgroup	IPTc N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
3.1.1 During intervention (SP)						
Dicko 2008	116	116	-0.6 (0.11)		52.88%	0.55[0.45,0.69]
Kweku 2008	562	613	-0.4 (0.12)		47.13%	0.68[0.54,0.86]
Subtotal (95% CI)					**100%**	**0.61[0.5,0.74]**
Heterogeneity: Tau^2=0.01; Chi^2=1.51, df=1(P=0.22); I^2=33.75%						
Test for overall effect: Z=4.97(P<0.0001)						
3.1.2 During intervention (SP+AQ)						
Dicko 2011	1481	1485	-1.8 (0.09)		46.69%	0.17[0.14,0.2]
Konate 2011	1504	1494	-1.2 (0.05)		48.67%	0.29[0.26,0.32]
Sesay 2011	513	533	-1.1 (1.12)		4.64%	0.34[0.04,3.05]
Subtotal (95% CI)					**100%**	**0.23[0.14,0.37]**
Heterogeneity: Tau^2=0.13; Chi^2=26.56, df=2(P<0.0001); I^2=92.47%						
Test for overall effect: Z=5.84(P<0.0001)						
3.1.3 During intervention (SP+AS)						
Cissé 2006	435	437	-2 (0.18)		100%	0.14[0.1,0.2]
Subtotal (95% CI)					**100%**	**0.14[0.1,0.2]**
Heterogeneity: Not applicable						
Test for overall effect: Z=10.94(P<0.0001)						
3.1.4 During intervention (AQ+AS)						
Kweku 2008	594	613	-1.3 (0.17)		100%	0.26[0.19,0.37]
Subtotal (95% CI)					**100%**	**0.26[0.19,0.37]**

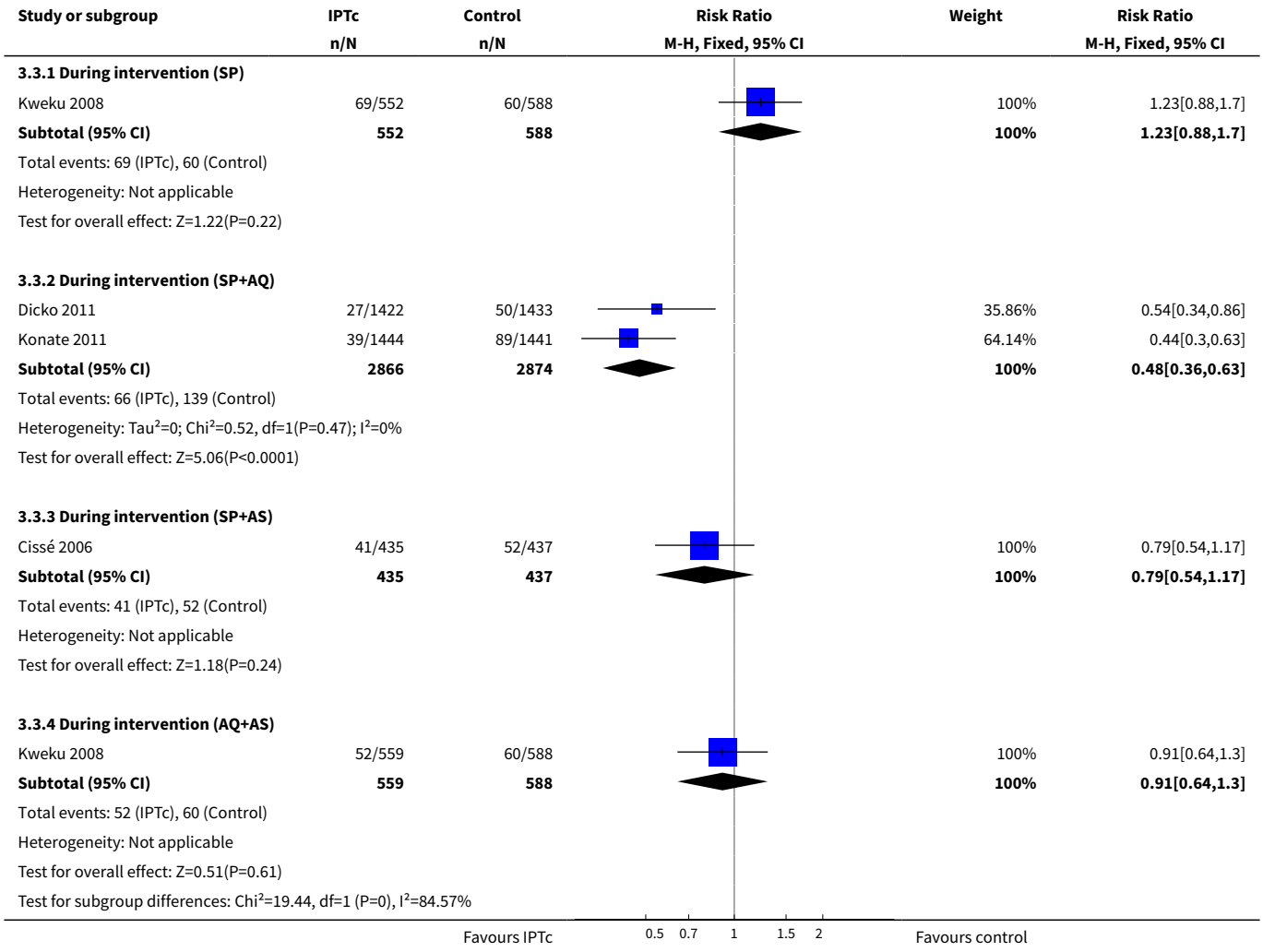
Favours IPTc — Favour control



Analysis 3.2. Comparison 3 IPTc versus placebo or no IPTc (subgroup analysis: type of antimalarial drug), Outcome 2 Parasitaemia.



Analysis 3.3. Comparison 3 IPTc versus placebo or no IPTc (subgroup analysis: type of antimalarial drug), Outcome 3 Moderately severe anaemia.



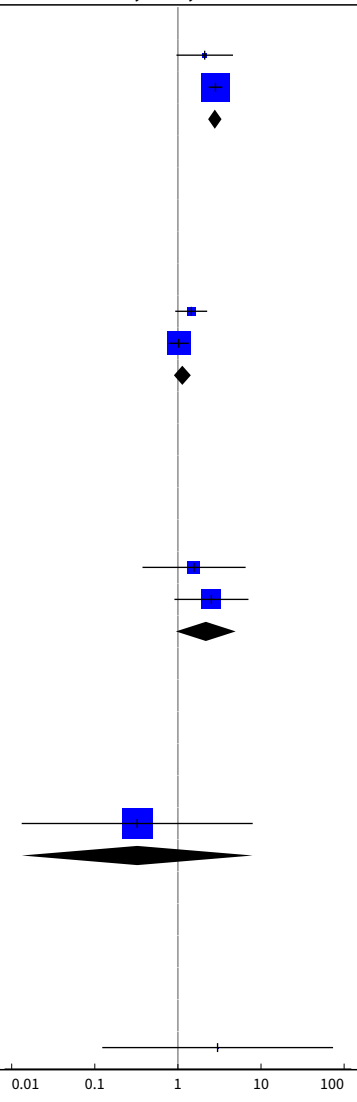
Comparison 4. IPTc (SP +AQ) versus placebo or no IPTc

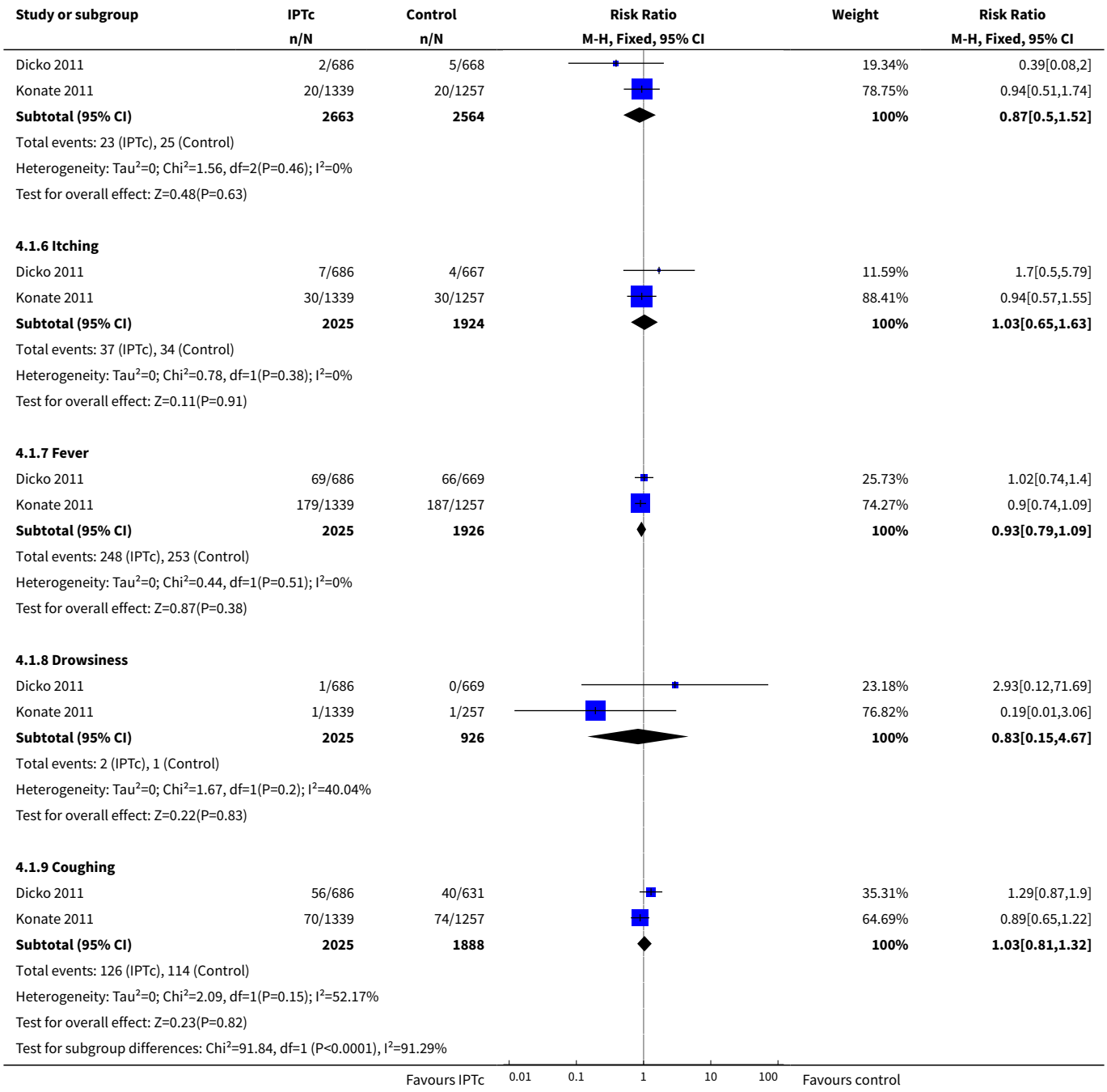
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Non-serious adverse events (during intervention)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Vomiting	2	3544	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [2.31, 3.35]
1.2 Diarrhoea	2	3951	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.90, 1.43]
1.3 Loss of appetite	2	3950	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [0.95, 4.96]
1.4 Jaundice	1	1353	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.94]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.5 Skin rash	3	5227	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.50, 1.52]
1.6 Itching	2	3949	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.65, 1.63]
1.7 Fever	2	3951	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.09]
1.8 Drowsiness	2	2951	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.15, 4.67]
1.9 Coughing	2	3913	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.81, 1.32]

Analysis 4.1. Comparison 4 IPTc (SP +AQ) versus placebo or no IPTc, Outcome 1 Non-serious adverse events (during intervention).

Study or subgroup	IPTc n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Vomiting					
Dicko 2011	19/475	9/473		6.69%	2.1[0.96,4.6]
Konate 2011	368/1339	122/1257		93.31%	2.83[2.34,3.42]
Subtotal (95% CI)	**1814**	**1730**		**100%**	**2.78[2.31,3.35]**
Total events: 387 (IPTc), 131 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.53, df=1(P=0.47); I^2=0%					
Test for overall effect: Z=10.88(P<0.0001)					
4.1.2 Diarrhoea					
Dicko 2011	46/686	31/669		25.69%	1.45[0.93,2.25]
Konate 2011	96/1339	88/1257		74.31%	1.02[0.77,1.35]
Subtotal (95% CI)	**2025**	**1926**		**100%**	**1.13[0.9,1.43]**
Total events: 142 (IPTc), 119 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.68, df=1(P=0.2); I^2=40.39%					
Test for overall effect: Z=1.04(P=0.3)					
4.1.3 Loss of appetite					
Konate 2011	5/1339	3/1257		37.92%	1.56[0.37,6.53]
Dicko 2011	13/686	5/668		62.08%	2.53[0.91,7.06]
Subtotal (95% CI)	**2025**	**1925**		**100%**	**2.17[0.95,4.96]**
Total events: 18 (IPTc), 8 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=1.83(P=0.07)					
4.1.4 Jaundice					
Dicko 2011	0/686	1/667		100%	0.32[0.01,7.94]
Subtotal (95% CI)	**686**	**667**		**100%**	**0.32[0.01,7.94]**
Total events: 0 (IPTc), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
4.1.5 Skin rash					
Sesay 2011	1/638	0/639		1.91%	3[0.12,73.62]





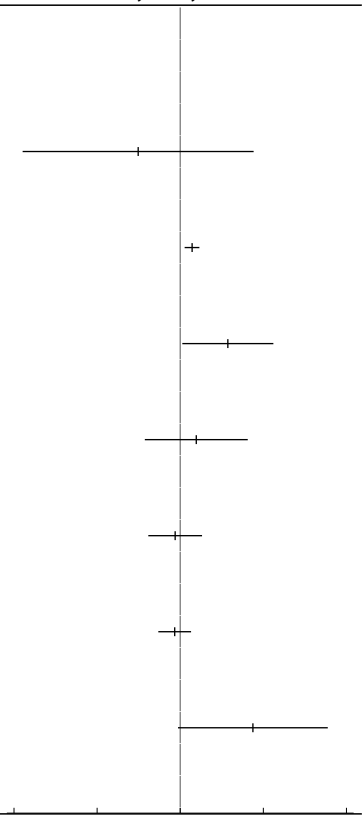
Comparison 5. IPTc (AS+SP) versus placebo or no IPTc

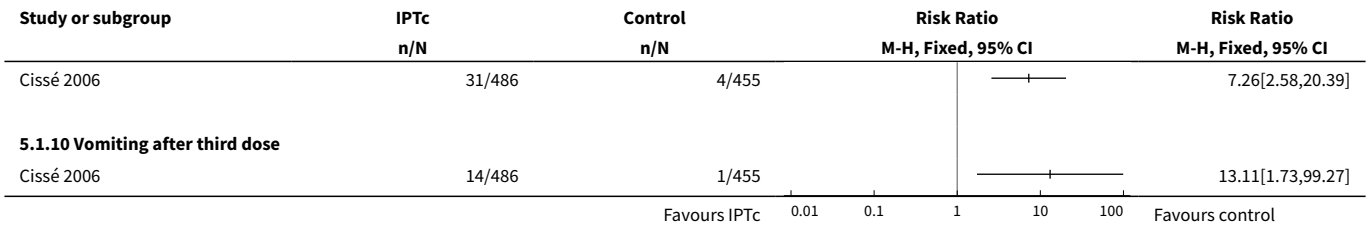
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-serious adverse events (during intervention)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Severe skin or neurological reaction	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.2 Convulsions	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Nervousness	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Pruritus	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Minor skin rash	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 Dizziness	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.7 Diarrhoea	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.8 Vomiting after first dose	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.9 Vomiting after second dose	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.10 Vomiting after third dose	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 IPTc (AS+SP) versus placebo or no IPTc, Outcome 1 Non-serious adverse events (during intervention).

Study or subgroup	IPTc n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
5.1.1 Severe skin or neurological reaction				
Cissé 2006	0/486	0/455		Not estimable
5.1.2 Convulsions				
Cissé 2006	0/486	1/455		0.31[0.01,7.64]
5.1.3 Nervousness				
Cissé 2006	163/486	110/455		1.39[1.13,1.7]
5.1.4 Pruritus				
Cissé 2006	12/486	3/455		3.74[1.06,13.18]
5.1.5 Minor skin rash				
Cissé 2006	5/486	3/455		1.56[0.38,6.49]
5.1.6 Dizziness				
Cissé 2006	13/486	14/455		0.87[0.41,1.83]
5.1.7 Diarrhoea				
Cissé 2006	33/486	36/455		0.86[0.54,1.35]
5.1.8 Vomiting after first dose				
Cissé 2006	8/486	1/455		7.49[0.94,59.65]
5.1.9 Vomiting after second dose				





ADDITIONAL TABLES

Table 1. IPTc (AS+AQ) versus placebo or no IPTc: Non-serious adverse events (during intervention)

	Prevention	Treatment	
IPTc	**HMM**	**IPTc**	
Adverse event	(*N* = 429)	(*N* = 86)	(*N* = 64)
Dark urine	5.4 (23)	4.7 (4)	0 (0)
Dizziness	0.9 (4)	1.2 (1)	3.1 (2)
Dysphagia	0 (0)	0 (0)	0 (0)
Headache	2.6 (11)	1.2 (1)	6.3 (4)
Itching	2.6 (11)	1.2 (1)	1.6 (1)
Jaundice	0 (0)	2.3 (2)	0 (0)
Nausea	0.5 (2)	1.2 (1)	0 (0)
Palpitation	0 (0)	0 (0)	0 (0)
Skin rash	1.4 (6)	7.0 (6)	0 (0)
Sought medical attention	1.2 (5)	4.7 (4)	3.1 (2)
Sleeplessness	2.6 (11)	15.1 (13)	3.1 (2)
Sore mouth	0 (0)	0 (0)	4.7 (3)
Vomiting	0.7 (3)	2.3 (2)	0 (0)
Weakness	3.0 (13)	7.0 (6)	3.1 (2)
Other	2.1 (9)	1.2 (1)	1.6 (1)

Data reported by Tagbor 2011 but does not adjust for clustering.

APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	malaria	malaria	MALARIA	MALARIA	malaria
2	prophylaxis	prophylaxis	malaria	malaria	prophylaxis
3	intermittent treatment	intermittent treatment	1 or 2	1 or 2	prevention
4	—	presumptive treatment	prophylaxis	prophylaxis	2 or 3
5	—	2 or 3 or 4	chemoprophylaxis	chemoprophylaxis	1 and 4
6	—	1 and 5	prevention	prevention	—
7	—	—	intermittent treatment	intermittent treatment	—
8	—	—	presumptive treatment	presumptive treatment	—
9	—	—	4 or 5 or 6 or 7 or 8	4 or 5 or 6 or 7 or 8	—
10	—	—	3 and 9	3 and 9	—

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2006); upper case: MeSH or EMTREE heading; lower case: free text term.

Appendix 2. GRADE profile 1

Question: Does IPTc reduce all-cause mortality and malaria morbidity in children aged < 5 years?

Setting: Areas with marked seasonal malaria transmission

Quality assessment						No of events/patients		Effect		Quality	Importance
№ of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPTc	Control	Relative (95% CI)	Absolute		
Clinical malaria												
6	randomized trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness[3]	no serious imprecision[4]	none	0.7 episodes per child per year	2.5 episodes per child per year[5]	Rate Ratio 0.26 (0.17 to 0.38)	1.8 fewer episodes per child per year (from 1.6 fewer to 2.1 fewer)	⊕⊕⊕⊕ HIGH	Critical
Severe malaria												
2	randomized trials	no serious risk of bias[6]	no serious inconsistency	no serious indirectness[7]	no serious imprecision[4]	none	9 episodes per 1000 children per year	35 episodes per 1000 children per year[8]	Rate Ratio 0.27 (0.1 to 0.76)	26 fewer episodes per 1000 children per year (from 8 fewer to 31 fewer)	⊕⊕⊕⊕ HIGH	Critical
Death from any cause												
6	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[3]	serious[9]	none	10/4751 (0.21%)	16/4782 (0.33%)[10]	RR 0.66 (0.31 to 1.39)	1 fewer per 1000 (from 2 fewer to 1 more)	⊕⊕⊕ MODERATE	Important
Moderately severe anaemia												
5	randomised trials	no serious risk of bias	serious[11]	no serious indirectness	no serious imprecision	none	203/4373 (4.6%)	296/4432 (6.7%)[10]	RR 0.71 (0.52 to 0.98)	19 fewer per 1000 (from 1 fewer to 32 fewer)	⊕⊕⊕ MODERATE	Important
Serious drug-related adverse event												
6	randomized trials	no serious risk of bias[1]	no serious inconsistency[12]	no serious indirectness[3]	serious[13]	none	4751	4782	-	-	⊕⊕⊕ MOD-	Important

(Continued)

										ER-ATE	
Non-serious adverse event											
6 randomized trials	serious[14]	no serious inconsistency	no serious indirectness[3]	no serious imprecision	none4751	4782	-	-		⊕⊕⊕ MODERATE	important

[1] The studies were well conducted with allocation concealment at low risk of bias in all studies, and 5 out of 6 studies were blinded and used placebos.
[2] There was substantial heterogeneity between these 6 trials. All 6 trials showed a statistically significant benefit but the magnitude of this benefit was variable. Not downgraded.
[3] The included trials were conducted in Ghana, Mali (2), The Gambia, Senegal and Burkina Faso, in areas described as 'seasonal malaria transmission'. Most studies were limited to pre-school aged children. Three studies administered monthly AQ+SP, two studies used bimonthly SP, and one study used monthly SP + AS.
[4] There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.
[5] The incidence of malaria in the control groups was 2.25 episodes per child per year in Senegal, 2.4 in Mali, and 2.88 in Burkina Faso.
[6] These two trials were well conducted and at low risk of bias.
[7] These trials were conducted in areas of seasonal transmission in Mali and Burkina Faso. Both trials compared SP+AQ with placebo in pre-school age children. Of note, LLITN use was high in both the intervention and control groups in both studies.
[8] The incidence of severe malaria in the control groups was 37 per 1,000 children per year in Mali, and 32 per 1,000 children per year in Burkina Faso
[9] Downgraded by 1 for imprecision: There were very few deaths in these trials, and none of the trials were adequately powered to detect an effect on mortality. Larger trials are necessary to have confidence in this effect. However, a reduction in death would be consistent with the high quality evidence of a reduction in severe malaria.
[10] These control group risks are taken from the sum of events and participants in the included trials.
[11] There was substantial heterogeneity between these 5 trials and the trials from Ghana and The Gambia did not show an effect. Downgraded by 1 for Inconsistency. There was no reason to downgrade for study limitations, directness or precision.
[12] All six trials reported that there was no case of drug-related serious adverse event. One trial reported that four participants were withdrawn from the treatment arm: two cases for non-severe skin rash, one for itching and another for acute respiratory infection. One trial reported skin eruptions with macular hyper-pigmentation which was neither Stevens Johnson syndrome nor any other form of severe skin lesions.
[13] Downgraded by 1 under precision. Trials of this size are underpowered to fully detect or exclude rare serious adverse events. Observation should continue once implemented.
[14] Downgraded by 1 under study limitations. All seven trials commented on observed adverse events. However, the thoroughness of the methods used to collect these data are incomplete in some of these trials. The only adverse event found to be statistically more common with IPTc was vomiting after AQ+SP (see Appendix 5).

Appendix 3. GRADEprofile 2

Question: Is IPTc still effective where ITN coverage is high?

Setting: Areas with marked seasonal transmission

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPTc	Control	Relative (95% CI)	Absolute		
Clinical malaria - (where bed-nets are also used)												
2	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision[3]	none	0.6 episodes per child per year	2.5 episodes per child per year[4]	Rate Ratio 0.22 (0.13 to 0.38)	1.9 fewer per child per year (from 1.6 fewer to 2.2 fewer)	⊕⊕⊕⊕ HIGH	Critical
Severe malaria												
2	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision[3]	none	9 episodes per 1000 children per year	35 episodes per 1000 children per year[5]	Rate Ratio 0.25 (0.1 to 0.68)	26 fewer episodes per 1000 children per year (from 11 fewer to 32 fewer)	⊕⊕⊕⊕ HIGH	Critical

[1] These trials were well conducted and considered at low risk of bias.
[2] Two trials compared IPTc with placebo where both groups were also given insecticide treated bednets (ITNs). These trials were conducted in Mali and Burkina Faso. ITN usage was over 99% in both groups in Mali, and 92% in both groups in Burkina Faso.
[3] There was no reason to downgrade for study limitations, insistency, directness or precision.
[4] The incidence of malaria in the control groups was 2.4 in Mali, and 2.88 in Burkina Faso.
[5] The incidence of severe malaria in the control groups was 37 per 1,000 children per year in Mali, and 32 per 1,000 children per year in Burkina Faso

Appendix 4. GRADEprofile 3

Question: Is IPTc still effective where home-based management of malaria is practiced?

Setting: Areas with marked seasonal transmission

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPTc	Control	Relative (95% CI)	Absolute		
Clinical malaria - (where home-based management of malaria is used)												
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	none	0.2 episodes per child per year	0.5 episodes per child per year[4]	Rate Ratio 0.34 (0.04 to 3.05)	0.3 fewer episodes per child per year (0.5 fewer to 1.0 more)	⊕⊕ LOW	Critical
Severe malaria - Not reported												
0	-	-	-	-	-	-	-	-	-	-	–	Critical

[1] Downgraded by 1 for risk of bias: This trial did not adequately describe the methodology to make judgements about the risk of bias.
[2] One trail conducted in Ghana compared IPTc with no IPTc in the context of an on-going programme of home-based management of malaria.
[3] Downgraded by 1 for imprecision: The result is not statistically significant.
[4] The incidence of febrile episodes (treated presumptively as malaria) in the control group was lower in this trial than seen elsewhere.

Appendix 5. GRADEprofile 4

Question: Is amodiaquine plus sulfadoxine-pyrimethamine an effective and safe option for IPTc?

Setting: Areas with marked seasonal transmission

Quality assessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AQ+SP	Control	Relative (95% CI)	Absolute		
Clinical malaria												
3	randomized trials	no serious risk of bias[1]	no serious inconsistency[2]	no serious indirectness[3]	no serious imprecision[4]	none	0.6 episodes per child per year	2.5 episodes per child per year[5]	Rate Ratio 0.23 (0.14 to 0.37)	1.9 episodes fewer per child per year (from 1.6 fewer to 2.2 fewer)	⊕⊕⊕⊕ HIGH	Critical
Severe malaria												
2	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[6]	no serious imprecision[7]	none	9 episodes per 1000 children per year	35 episodes per 1000 children per year[8]	Rate Ratio 0.27 (0.1 to 0.76)	26 fewer episodes per 1000 children per year (from 8 fewer to 31 fewer)	⊕⊕⊕⊕ HIGH	Critical
Death from any cause												
3	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[3]	serious[9]	none	6/3498 (0.17%)	10/3512 (0.28%)[10]	RR 0.62 (0.23 to 1.65)	1 fewer per 1000 (from 2 fewer to 2 more)	⊕⊕⊕ MODERATE	Important
Moderately severe anaemia												
2	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[6]	no serious imprecision[7]	none	66/2866 (2.3%)	139/2874 (4.8%)[10]	RR 0.48 (0.36 to 0.63)	25 fewer per 1000 (from 18 fewer to 31 fewer)	⊕⊕⊕⊕ HIGH	Important
Serious drug-related adverse event												
3	randomized trials	no serious risk of bias[1]	no serious inconsistency[11]	no serious indirectness[3]	serious[12]	none	-	-	-	-	⊕⊕⊕ MODERATE	Important

(Continued)

Non-serious adverse events- vomiting

2 randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[6]	no serious imprecision[7]	none	387/1814 (21.3%)	131/1730 (7.6%)[10]	RR 2.78 (2.31 to 3.35)	135 more per 1000 (from 99 more to 178 more)	⊕⊕⊕⊕ HIGH	Important

[1] The studies were well conducted with allocation concealment at low risk of bias in all studies, and all studies were blinded and used placebos.
[2] There was substantial heterogeneity between these 3 trials. All 3 trials showed a trend to favour IPTc but the magnitude of this benefit was variable. Not downgraded.
[3] Two trials compared IPTc with placebo where both groups were also given insecticide treated bednets (ITNs). These trials were conducted in Mali and Burkina Faso. ITN usage was over 99% in both groups in Mali, and 92% in both groups in Burkina Faso. The third trial was conducted in the Gambia. All were in pre-school age children, and administered monthly SP+AQ.
[4] There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.
[5] The incidence of malaria in the control groups was 2.4 in Mali, and 2.88 in Burkina Faso.
[6] These trials were conducted in areas of seasonal transmission in Mali and Burkina Faso.
[7] There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.
[8] The incidence of severe malaria in the control groups was 37 per 1,000 children per year in Mali, and 32 per 1,000 children per year in Burkina Faso
[9] Downgraded by 1 for imprecision: There were very few deaths in these trials, and none of the trials were adequately powered to detect an effect on mortality. Larger trials are necessary to have confidence in this effect. However, a reduction in death would be consistent with the high quality evidence of a reduction in severe malaria.
[10] These control group risks are taken from the sum of events and participants in the included trials.
[11] All three trials reported that there was no case of drug-related serious adverse event. One trial reported that four participants were withdrawn from the treatment arm: two cases for non-severe skin rash, one for itching and another for acute respiratory infection. One trial reported skin eruptions with macular hyper-pigmentation which was neither Stevens Johnson syndrome nor any other form of severe skin lesions.
[12] Downgraded by 1 under precision. Trials of this size are underpowered to detect or exclude rare serious adverse events.

Appendix 6. GRADEprofile 5

Question: After stopping IPTc is there a rebound increase in all-cause mortality or malaria morbidity during the following malaria transmission season?

Setting: Areas with marked seasonal transmission

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPTc	Control	Relative (95% CI)	Absolute		
Clinical malaria												
3	randomized trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision[3]	none	2.5 episodes per child per year	2.5 episodes per child per year[4]	Rate Ratio 0.98 (0.82 to 1.17)	0 fewer episodes per child per year (from 0.5 fewer to 0.4 more)	⊕⊕⊕⊕ HIGH	Critical
Severe malaria - not reported												
0	-	-	-	-	-	-	-	-	-	-		Critical
Death from any cause												
1	randomized trials	no serious risk of bias[5]	no serious inconsistency	no serious indirectness[6]	serious[7]	none	8/594 (1.3%)	8/613 (1.3%)[8]	RR 1.03 (0.39 to 2.73)	0 more per 1000 (from 8 fewer to 23 more)	⊕⊕⊕ MODERATE	Important
Moderately severe anaemia												
1	randomized trials	no serious risk of bias[5]	no serious inconsistency	serious indirectness[9]	no serious imprecision	none	36/376 (9.6%)	47/392 (12%)[8]	RR 0.8 (0.53 to 1.2)	24 fewer per 1000 (from 56 fewer to 24 more)	⊕⊕⊕ MODERATE	Important

[1] These trials were well conducted and considered at low risk of bias.
[2] Three trials report clinical malaria during the following malaria season when IPTc was not given. These were conducted in Senegal, Mali, and Ghana.
[3] There was no reason to downgrade for study limitations, inconsistency, indirectness or imprecision.
[4] The incidence of malaria in the control groups was 2.25 episodes per child per year in Senegal, 2.4 in Mali, and 2.88 in Burkina Faso.
[5] This trial was well conducted and considered at low risk of bias.
[6] This trial was conducted in Ghana. A large reduction in clinical malaria was seen during the intervention period, following IPTc with either bimonthly sulfadoxine-pyrimethamine or amodiaquine plus artesunate.
[7] Downgraded by 1 for imprecision: there were very few deaths in these trials, and none of the trials were adequately powered to detect or exclude an effect on mortality. Larger trials are necessary to have confidence that there is no increase.
[8] These control group risks are taken from the sum of events and participants in the included trials.
[9] Downgraded by 1 for indirectness: only one trial reports the incidence of moderate anaemia during the following transmission season. This trial found no statistically significant benefit on anaemia during the administration of IPTc.

WHAT'S NEW

Date	Event	Description
13 January 2012	New citation required but conclusions have not changed	Significant update and changed focus
3 August 2011	New search has been performed	The original review has been split into two separate topics: "Intermittent treatment for malaria in children (IPTc) living in areas with seasonal transmission" and "Intermittent preventive treatment in infants". This update addresses a focused question on the potential benefit and harm of giving IPTc to children aged below five years living is areas with seasonal malaria transmission. Trials on continuous prophylaxis have been excluded.

HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 4, 2005

Date	Event	Description
22 August 2008	New search has been performed	Converted to new review format with minor editing.
20 February 2008	New citation required and conclusions have changed	2008, Issue 2: We included four new trials of intermittent treatment (Chandramohan 2005a; Cissé 2006; Macete 2006a; Kobbe 2007a). We removed quasi-randomized controlled trials from the inclusion criteria and excluded two such trials (Bradley-Moore 1985; Oyediran 1993) that were included in the Meremikwu 2005 version of this review. The evidence on benefits regarding reduction of malaria episodes, severe anaemia, and admissions remains strong and consistent with these changes. We also updated the analysis methods to stratify the individual and cluster-randomized trials. S Donegan and E Esu joined the author team, while P Garner and A Omari stepped down.

CONTRIBUTIONS OF AUTHORS

Martin Meremikwu, Ekpereonne Esu and Chioma Oringanje identified and extracted data from eligible trials for this update. Sarah Donegan, David Sinclair and Martin Meremikwu analysed the data, with Sarah Donegan playing the key role in handling the difficult statistical issues.

Martin Meremikwu prepared the first draft, and the other authors read through and made input to all sections of the review. David Sinclair and Martin Meremikwu developed the GRADE profiles and summary of findings tables.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Calabar, Nigeria.
- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This version of the review differs from the first protocol and previous versions (Meremikwu 2002, Meremikwu 2005, Meremikwu 2008), because it includes only trials that administered short duration (monthly or every two months) antimalarial treatments as IPTc to preschool children living in areas with seasonal malaria transmission. Unlike the earlier versions, it excluded trials on prolonged daily or weekly chemoprophylaxis and those that gave IPT to only, or predominantly, infants.

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia [epidemiology] [prevention & control]; Antimalarials [*administration & dosage]; Endemic Diseases [*prevention & control] [statistics & numerical data]; Insecticide-Treated Bednets; Malaria [epidemiology] [mortality] [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Child, Preschool; Humans; Infant